Health Canada Santé Canada

Memorandum: Human Health Soil Screening Values (SSVs) for Perfluorooctane Sulfonate (PFOS)

Date: April 2016

Currently there are no Canadian Guidelines for PFOS in soil. In the absence of a soil quality guideline, Health Canada has developed soil screening values (SSVs) for PFOS, which can be used to determine whether the concentrations detected are likely to be of concern to human health. Screening values are developed at the request of a federal department in the event of spill, leak or other contamination event, and are based on the available scientific studies. They are not subject to a review as thorough as the CCME Soil Quality Guidelines, which undergo internal peer review and public consultation before being approved by the CCME. Soil screening values are provided as guidance, and apply to soil which humans may be exposed. Health Canada continues to monitor new research in this area.

Although the approach used for developing soil screening values is generally consistent with the CCME protocol for development of soil quality guidelines for direct contact with soil (CCME 2006) these soil screening values should not be considered as draft CCME guidelines.

The advice herein is, is intended for use at federal sites, and has been provided to meet the needs of federal custodians at this time. It is not intended for use in any other context. The advice herein may change as more information becomes available regarding the toxicity of PFOS and as environmental quality guidelines are developed. Any decisions taken based on the advice provided herein are the responsibility of Federal Custodians making those decisions.

Soil screening values for residential, commercial and industrial land uses are presented. The custodian should determine the most appropriate value for application at a site based on site use. Further information on the land use scenarios and default assumptions can be found in CCME (2006).

SSVs and supporting guidance may change without notice. Please check for published values and confirm these values are appropriate for use prior to use.

Table 1: Soil Screening Values for PFOS

Land Use	Residential/Parkland	Commercial	Industrial/Commercial without Toddler
Soil Screening Value (mg/kg)	2.1[a]	3.2[a]	30.5[b]

[a]: Based on direct contact with soil;

[b]: Based on off-site migration.

Notes:

- The SSV for the protection of potable groundwater could not be calculated due to insufficient data. Concerns about PFOS in groundwater used as drinking water should be addressed on a site specific basis.
- The SSV check value for consumption of produce, meat and milk could not be calculated due to insufficient data. Concerns regarding consumption of foods and PFOS should be addressed on a site specific basis.
- Since PFOS is essentially non-volatile, the inhalation of indoor air check was not calculated.

Canada

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1.0 INTRODUCTION

Perfluorooctane sulfonate (PFOS) is an anthropogenic chemical that is present in the environment as the result of a broad range of applications including, but not limited to, its use in manufacturing processes and consumer products. The Government of Canada concluded that PFOS, its salts, and precursors are or may be entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity based on risk assessment activities conducted under the Canadian Environmental Protection Act (CEPA; 1999),. PFOS, its salts, and precursors were added to Schedule 1 of CEPA (1999), the List of Toxic Substances. PFOS and its salts were also added to the Virtual Elimination List compiled under CEPA.

Historically, PFOS and other perfluoroalkyl substances (PFAS) were present in aqueous film forming foams (AFFFs) which were typically used during firefighting training activities carried out at firefighting training areas (FFTAs) at airports and military bases across the country. As a result, PFOS and other PFA concentrations in the environment may be elevated at historic FFTAs where AFFFs were used.

The purpose of this document is to provide custodians with health-based soil screening values (SSVs) to be used to screen for contaminants of potential concern (COPCs) at federal contaminated sites Currently, there are no approved Canadian environmental quality guidelines for the protection of human health for PFOS and the availability of PFOS guidelines and standards from other jurisdictions is limited. For example, the United States Environmental Protection Agency (US EPA) Region 4 developed a human health based soil screening level for specific regional application, and the Minnesota Department of Health developed a provisional drinking water guideline to address groundwater quality issues in industrial areas of the state. Similarly, there are no toxicological reference values (TRVs) for PFOS. The current document summarizes the derivation of proposed toxicological reference values (TRVs) based on the available toxicological data and provides SSVs based on these TRVs.

Health Canada is in the process of developing Soil Quality Guidelines through the Canadian Council of Ministers of the Environment (CCME) and Guidelines for Canadian Drinking Water Quality through the Federal-Provincial-Territorial Committee on Drinking Water. To meet immediate needs, human health-based values for drinking water (including groundwater when used as a drinking water source) and for soil quality have been prepared by Health Canada to assist federal custodians in the assessment of PFOS in these media at federal contaminated sites. These values are based on a limited review of available information and have not been formally vetted or peer reviewed. The resultant uncertainty and limitations associated with the use of these values are discussed herein.

This document provides the following:

- background information;
- environmental fate and behaviour;
- behaviour and effects in human and mammalian species;
- derivation of TRVs; and
- derivation of human health SSVs.

2.0 METHODOLOGY

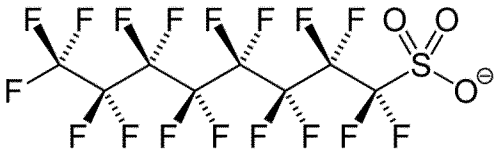
The calculation of the SSVs and the preparation of the supporting documentation were completed following the methods described in the CCME's A Protocol for the Derivation of Environmental and Human Health Soil Quality Guidelines (CCME 2006). Health Canada provided additional supporting documents, including Sanexen Environmental Services Inc. (Sanexen 2015) to assist with the derivation of the SSVs.

3.0 BACKGROUND INFORMATION

3.1 Chemical Structure and Identity

The information below is reproduced from Health Canada 2016.

PFOS is an anthropogenic compound with a chain length of eight perfluorinated carbons. PFOS, its salts and its precursors form part of a larger chemical class of fluorochemicals typically referred to as perfluorinated alkyl acids (PFAA). PFOS can occur in several forms, including the acid ($C_8HF_{17}SO_3$; 500.03 g/mol; CAS number 1763-23-1), the potassium salt (K^+PFOS; 538.23 g/mol; CAS number 2795-39-3), the ammonium salt ($NH4^+$ PFOS; CAS number 29081-56-9), the diethanolamine salt ($C_8F_{17}SO_3NH$; CAS number 70225-14-8), and the lithium salt (Li^+PFOS; CAS number 29457-72-5). The main synonyms of PFOS are 1-perfluorooctanesulfonic acid, heptadecafluoro-1-octanesulfonic acid, heptadecafluorooctan-1-sulphonic acid, perfluorooctylsulfonic acid and 1-octanesulfonic acid (Agency for Toxic Substances and Disease Registry [ATSDR] 2009). The chemical structure for PFOS is illustrated below.



3.2 Physical and Chemical Properties

The information below is reproduced from Health Canada 2016.

PFOS is soluble in water, with solubility values reported at 570 mg/L and 519 mg/L (at 20°C) in pure water (OECD 2002; Brooke et al. 2004) and at 370 mg/L in freshwater (OECD 2002). The solubility of PFOS decreases when the water salt content increases (OECD 2002). The solubility depends on the acid dissociation constant (pKa) of the acid form; the pKa value for PFOS has been estimated at -3.27 (no direct measurement of the pKa has been located) and PFOS is considered to be a strong acid, suggesting that the environmental partitioning of PFOS will be dominated by the anionic form (Brooke et al. 2004).

PFOS contains both hydrophobic and hydrophilic functional groups and is thus expected to behave differently than traditional hydrophobic chemicals. Due to its surfactant properties, the octanol:water partition coefficient (Log Kow) cannot be determined directly because multiple layers are formed in octanol:water. Moreover, the parameters usually estimated from the Kow (e.g., Koc, Kd, bioconcentration factor) cannot be calculated using this method (OECD 2002), nor using conventional quantitative structure-activity relationship models (Beach et al. 2006).

PFOS is essentially non-volatile, with a vapour pressure of 3.27×10^{-9} atm at 20°C (OECD 2002; Brooke et al. 2004; ATSDR 2009) and its Henry's Law constant was estimated to be approximately 3.1×10^{-9} atm-m^3/mol. Attempts to measure the air–water partition coefficient using the potassium salt do not indicate

volatilization to any measurable extent. The air-water partition coefficient was thus considered to be $<2 \times 10^{-6}$, and to be essentially zero (OECD 2002; Brooke et al. 2004). Nevertheless, some of the PFOS-containing substances have considerably higher vapour pressure and are more likely to be volatile. This may allow the wider transport of potential PFOS precursors through the air than for PFOS itself (Brooke et al. 2004).

3.3 Geochemical Occurrence

PFOS is chemically synthesized and does not occur naturally.

3.4 Analytical Methods

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High-performance liquid chromatography mass spectrometry (HPLC MS/MS) or liquid chromatography/mass spectrometry (LC-MS) methods are commonly used to detect perfluoroalkyls (Weremiuk et al. 2006; Wilson et al. 2007; Zhao et al. 2007; Lindstrom et al. 2011). Gas chromatography mass spectrometry (GC-MS) combined with derivatization and LC-MS or with tandem MS (LC-MS/MS also known as the triple quadrupole MS) can also be used to quantify fluorinated surfactants in environmental media such as water, wastewater, sewage sludge and biota (Meesters and Schröder 2004; Weremiuk et al. 2006).

Strynar et al. (2012) described a method for analyzing perfluoroalkyl substances (PFAS) in surface soils using methanol extraction followed by ultra-high pressure liquid chromatography with tandem mass spectrometry (UPLC-MS/MS), and using six point calibration curves for each PFAS analyte. The authors noted the need to develop PFAS standard reference material to compare analytical methods (Strynar et al. 2012).

Sampling for PFAS should follow recent guidance to ensure that samples are representative.

The information below is reproduced from Health Canada, 2016.

In spite of the significant improvements in the analytical methods for the determination of PFAS in environmental water samples, challenges, uncertainties and drawbacks still remain. Major challenges associated with the trace quantitation of PFAS include matrix effects and background contamination in the analytical blanks. In order to generate accurate data, quality control procedures (matrix spikes, duplicates, spike-recovery experiments, surrogate recovery checks) are critical. In addition, the use of isotope-labelled internal standards is a standard practice and must be used in the analysis of PFAS.

3.5 Production, Use and Discharge to the Environment

The information below is reproduced from Health Canada 2016.

The principal applications of PFOS were for water, oil and/or stain resistance on surface and paper-based applications, such as rugs and carpets, fabric and upholstery. PFOS was also used in specialized chemical applications, such as fire-fighting foams, hydraulic fluids, carpet spot removers, mining and oil well surfactants and other specialized chemical formulations (OECD 2002; Health Canada 2006). PFOS was produced in the US until 2002, when the 3M Company phased out its PFOS production (ATSDR 2009). Although there are no known Canadian manufacturers of PFAA, including PFOS, almost 600,000 kg of PFAA were imported into Canada between 1997 and 2000 (PFOS represented a very small proportion of this total) (Health Canada 2006). In 2009, PFOS and its salts were added to the Canadian Virtual Elimination List compiled under subsection 65(2) of CEPA 1999, as required by subsection 3(1) of the Act (SOR/2009-15)

(Government of Canada 2009). The Canadian regulations prohibit the manufacture, import, sale, offer for sale and use of PFOS or products containing PFOS, unless incidentally present, with certain exemptions for aviation hydraulic fluids under certain conditions, and some products used in photographic or photolithographic process (Government of Canada 2008).

3.6 Sources and Concentrations in Environmental Media

Canadians can be exposed to perfluorinated compounds present in food, consumer products, dust, and drinking water (Tittlemier et al. 2007). The major sources of PFAA are expected to be food and consumer products, including solution-treated carpeting and treated apparel (Tittlemier et al. 2007).

The estimated total daily intake of PFAA (estimates not provided for individual PFAA) in Canadians was reported to be 410 ng/day for the general population of Canada (Tittlemier et al. 2007). A summary of concentrations in different media are presented in the sections below.

3.6.1 Water

The information below is reproduced from Health Canada 2016.

Although PFOS is not regularly monitored at drinking water treatment plants in Canada, the chemical analysis has been performed for a few locations. PFOS was not detected (method detection limit [MDL] 0.85 ng/L) in raw or finished water from samples obtained in 2012 from two drinking water treatment plants in Calgary (Alberta Environment and Water 2013). In Quebec, raw and treated water samples were obtained monthly from seven sites between April 2007 and March 2008 (a total of 84 samples each of raw and treated water). PFOS was detected in 52% of treated samples (MDL of 0.3–0.6 ng/L), with a median value of 1.0 ng/L. The detection rate and median concentrations were higher in treated water than in raw water, for which the detection rate and median were 40% and <1 ng/L, respectively (Ministère du Développement durable, de l'Environnement, de la Faune et des Parcs 2012). The reported PFOS concentration in 5 tap water samples from Niagara-on-the-Lake, Ontario was 3.3 ng/L (Mak et al. 2009).

As part of a national survey of emerging contaminants in drinking water (including PFOS) conducted by Health Canada, treated and raw water were monitored in winter and summer at 35 locations in 2009 and 30 locations in 2010. In the four sampling periods, only one sample contained PFOS above the MDL of 0.077 ng/L; the PFOS concentration in that sample was 0.082 ng/L, and was obtained in the winter of 2009 (Health Canada 2013a).

3.6.2 Food

The information below is reproduced from Health Canada 2016.

Food is generally considered to be the main source of PFOS exposure for the majority of the Canadian population, but exposure from food is still well below what is considered unsafe to humans. PFOS was measured in a selection of Canadian food composite samples (samples from the Canadian Total Diet Study conducted in 2004 and additional samples collected between 1992 and 2001) to estimate dietary intake (Tittlemier et al. 2007). PFOS was detected in 7 out of 54 food composites (average detection limit: 0.5 ng/g). The quantified concentrations ranged from 2.0 to 2.7 ng/g wet weight (w.w.; in marine and freshwater fish, ground beef and beef steak). Concentrations lower than the limit of quantitation were reported for microwave popcorn, luncheon meats and cold cuts, and freshwater fish. Measured data were used to estimate the average dietary daily exposure of Canadians and food was estimated to contribute 250 ng/day of PFAS, of which approximately 110 ng was attributed to PFOS (Tittlemier et al. 2007).

Store-bought and restaurant foods commonly consumed by Canadians were collected in Whitehorse (Yukon Territory, Canada) in 1998 and analyzed for PFAA (Ostertag et al. 2009a). PFOS was detected in only 2 samples (regular and processed cheese) and quantifiable in one sample (processed cheese: 1.14 ng/g w.w.; Ostertag et al. 2009a).

The marine ecosystem of the Eastern Canadian Arctic represents a source of food for the local population. In this region, the PFOS levels (on a w.w. basis) were reported to range from 0.28 to 1.8 ng/g w.w. in zooplankton and invertebrates, from 1.3 to 1.4 ng/g w.w. in fish, and from 2.4 to 122 ng/g in marine mammals (whales and pinnipeds) (Butt et al. 2010). The concentrations of PFAA in the traditional foods of Inuit in Northern Canada were measured in order to estimate their dietary exposure (Ostertag et al. 2009b). PFOS was detected in 39% of the 68 traditional food samples collected from Chesterfield Inlet, Igloolik, Pond Inlet and Qiqiktarjuak in Nunavut, between 1997 and 1999. PFOS was detected in both aquatic food (0.1–7.6 ng/g in ringed seal, polar bear (meat), beluga, narwhal, bearded seal, walrus, eider and black duck, or lake trout) and terrestrial food (5.0 ng/g in baked caribou liver, 0.1–0.2 ng/g in caribou bone marrow, heart, blood, kidney, stomach, tongue or meat). PFOS concentrations in the other samples (arctic char, seaweed, clams, ptarmigan, artic hare, snow goose, berries) were below the detection limit (<0.1 to <0.5 ng/g) (Ostertag et al. 2009b).

An Australian study quantified PFAA in food packaging and polytetrafluoroethylene (PEFT) sealant tape. PFOS was not detected in any of these samples, including in microwave popcorn bags (Dolman and Pelzing 2011).

3.6.3 Air

The information below is reproduced from Health Canada 2016.

In an assessment designed to estimate total daily intake of perfluorinated compounds in Canadians, the inhalation intake of PFOS was considered negligible due to its low volatility (Tittlemier et al. 2007).

The levels of PFAA in outdoor air were determined in a Canadian study conducted in 2007 in Vancouver (Shoeib et al. 2011). PFOS samples were collected using outdoor passive samplers deployed in residential yards for approximately 3 months. PFOS concentrations were below the detection limit (<0.02 pg/m^3) in all samples (n=6) (Shoeib et al. 2011). In another study, PFOS was detected in 4 out of 8 air samples (particulate-phase) collected over Lake Ontario, at concentrations varying between 2.5 and 8.1 pg/m^3. PFOS remained undetected in gaseous-phase samples (Boulanger et al. 2005). PFOS was also detected in the Canadian Arctic (Resolute Bay, Nunavut) with a mean concentration of 5.9 pg/m^3 in the gas and particulate phase of atmospheric air (2004 sampling) (Fromme et al. 2009, Butt et al. 2010).

In indoor air, the levels of PFOS mainly depend on PFOS concentration in air particulates and are thus related to PFOS levels in indoor dust, as well as the number, type and age of the potential sources (e.g., carpeting, furniture and paint) (Fraser et al. 2012). To date, data on indoor air concentrations of PFOS are limited to those reported in the aforementioned residential study (Shoeib et al. 2011). The authors collected PFOS in indoor air using passive samplers deployed for approximately 4 weeks in bedrooms of 59 participants. PFOS levels (available for 39 homes) were below the detection limit (<0.02 pg/m^3) in all samples (Shoeib et al. 2011).

3.6.4 Consumer Products

The information below is reproduced from Health Canada 2016.

Owing to the use patterns of PFOS, human exposure to PFOS would likely result from contact with, or the use of, certain consumer products (Health Canada 2006). Estimates of the contribution of solution-treated carpeting and treated apparel to Canadians' daily intakes of perfluorinated compounds were 120 ng/day and

12 ng/day, respectively (Tittlemier et al. 2007). PFOS has been measured in a variety of consumer products, including paint, printed circuit boards, carpet, leather, non-stick ware, and aqueous firefighting foams (Herzke et al. 2012).

3.6.5 Soil and Household Dust

The information below is reproduced from Health Canada 2016.

The estimated contribution of dust to Canadians' daily intakes of perfluorinated compounds was 28 ng/day (Tittlemier et al. 2007). The study did not estimate the total daily contribution of soil to perfluorinated compound exposure.

PFOS concentrations in dust in 67 Ottawa homes were between <4.6 and 5 065 ng/g, with a median value of 38 ng/g and a mean value of 444 ng/g (Kubwabo et al. 2005). House age and fraction of floor covering were reported to be significantly correlated with the concentration of PFAA in dust—older houses and those with smaller fractions of the floor covered with carpet were characterized by lower concentrations of PFAA (Kubwabo et al. 2005). In another Canadian study conducted in the City of Vancouver, PFOS was detected in all household dust samples analyzed for this compound (n=132). The PFOS concentrations ranged from 1.5 to 4,661 ng/g (median: 71 ng/g, mean: 280 ng/g) (Shoeib et al. 2011).

No studies reporting background PFOS levels in soils were found. Some data are available for soils surrounding perfluorochemical industrial facilities (as reviewed by ATSDR 2009).

3.6.6 Human Biomonitoring Data

The information below is reproduced from Health Canada 2016.

The Canadian Health Measures Survey (CHMS), Cycle 1 (2007–2009) indicates that PFOS plasma levels in adult males (geometric mean [GM]: 11.13 ng/mL; 95% CI: 10.03–12.36, 95th percentile: 31.31 ng/mL, n=1,376) are higher than in adult females (GM: 7.07 ng/mL; 95% CI: 6.30–7.93, 95th percentile: 20.05 ng/mL, n=1,504) (Health Canada 2010). This effect persisted in Cycle 2 of the study (2009–2011), which observed a decline in plasma concentrations compared with Cycle 1 (males-GM: 8.3 ng/mL, 95% CI: 7.4–9.3, 95th percentile: 19 ng/mL, n=511; Females-GM: 5.7 ng/mL, 95% CI: 4.9–6.6, 95th percentile: 19 ng/mL, n=506) (Health Canada 2013b).

PFOS was detectable in all serum samples (n=86) collected from 2006-2008 in a study of Inuit children attending childcare centers in Nunavik (Turgeon O'Brien et al. 2012). The geometric mean of PFOS in serum was 3.369 ng/mL with a range of 0.93–31 ng/mL. A separate study of 621 Nunavik Inuit adults reported PFOS serum levels of 0.480 to 470 ng/mL (GM: 18.28 ng/mL, 95% CI: 17.19–19.44 ng/mL) (Dallaire et al. 2009). Other Canadian studies have reported similar levels of PFOS in serum ranging from 3.7 to 63.1 ng/mL (Tittlemier et al. 2004; Kubwabo et al. 2004). Similar results have been shown elsewhere as the overall range of mean PFOS concentrations (in males or females) was from 1.7 to 73.2 ng/mL in serum samples collected from 10 countries (Kannan et al. 2004). PFOS concentrations in human serum/plasma collected worldwide (America, Asia, Australia, and Europe) over a period from 1998–2007. Mean PFOS concentrations ranged from 2.1 to 62 ng/mL in human serum/plasma collected worldwide (America, Asia, Australia, and Europe) from 1998–2007 (Ingelido et al. 2010). In the US, NHANES data for the period 2007–2008 indicate a median serum PFOS level of 13.6 ng/mL in the general population (≥12 years of age), with a downward temporal trend noted for the period 1999-2008 by Kato and colleagues (2011).

3.7 Summary of Existing Guidelines, Guidance Values or Screening Values

Soil and water quality guidelines and criteria established for PFOS in various jurisdictions are presented in the following table.

Table 2: Existing Soil and Water Criteria and Guidelines for PFOS in Canadian and Other Jurisdictions

Jurisdiction	Criterion/Guideline	Concentration	Reference
Soil			
United States, US EPA Region 4	Residential Soil Screening Level (SSL)	6 mg/kg	US EPA Region 4 2009
Water			
Canada	Guideline for Canadian Drinking Water Quality – In progress	0.6 µg/L	Health Canada 2016
United States, US EPA Region 4	Health Advisory (PHA) for drinking water	0.2 µg/L	US EPA Region 4 2009
United States, Minnesota	Groundwater Health Risk Limit	0.3 µg/L	Minnesota Pollution Control Agency 2009
	Chronic criterion for the protection of aquatic plants	19 µg/L	Minnesota Pollution Control Agency 2007
	Maximum criterion for the protection of aquatic organisms and plants	85 µg/L	
	Drinking water plus fish consumption criterion, and fish consumption criterion for Lake Calhoun, Minnesota	12 ng/L	
	Drinking water plus fish consumption criterion, and fish consumption criterion for Mississippi River	6 ng/L	
Netherlands	Proposed Maximum Permissible Concentration (MPC) for freshwater	0.65 ng/L	National Institute for Public Health and the Environment (RIVM) 2010
	Proposed drinking water MPC for surface water intended to be used as drinking water	0.53 µg/L	
	Proposed MPC for marine water	0.53 ng/L	
United Kingdom	Tier 1: Drinking water, no water concentration guideline	-	UK HPA 2012
	Tier 2: Drinking water, guideline limit where water companies are required to undertake water sampling and consult local health professionals	0.3 µg/L	
	Tier 3: Drinking water, guideline limit where water companies are required to implement measures to reduce concentrations below 1.0 µg/L as soon as is practicable	1.0 µg/L	
Germany	Health based Precautionary Value (HPV_1) – Composite PFOA/PFOS concentration	0.1 µg/L	Drinking Water Commission 2006
	Health based Guide Value for safe lifelong exposure of all population groups (GV) – Composite PFOA/PFOS concentration	0.3 µg/L	
	Precautionary Action Value for infants (PAV_i) – Composite PFOA/PFOS concentration	0.5 µg/L	
	Precautionary Action Value for adults (PAV_0) – Composite PFOA/PFOS concentration	5.0 µg/L	
Europe	Maximum Allowable Concentration (MAC) in inland surface waters	36 µg/L	European Commission 2012
	Maximum Allowable Concentration (MAC) in other surface waters	7.2 µg/L	

Source: Sanexen 2015

4.0 ENVIRONMENTAL FATE AND BEHAVIOUR

The information below is reproduced from Health Canada 2016.

The elevated water solubility of PFOS and the negligible volatility of its ionized species suggest that PFOS species will partition primarily to the aquatic environment. PFOS is a strong acid and tends to form strong bonds in soils, sediments, and sludge via a chemisorption mechanism (3M Company 2001; Brooke et al. 2004; Beach et al. 2006). Greater PFOS adsorption occurs under anaerobic conditions relative to aerobic conditions (Beach et al. 2006). PFOS does not partition into lipids but instead binds to certain proteins in animals (Beach et al. 2006). PFOS bioaccumulates in tissues of aquatic and terrestrial living organisms including humans. Data for the marine food web from the Eastern Canadian Arctic (from 1996 to 2002) indicate that PFOS biomagnifies through the entire food web with a trophic magnification factor of 3.1 (Butt et al. 2010).

Under environmental conditions, PFOS does not hydrolyze, photolyze or biodegrade, and it is considered extremely persistent in the environment (OECD 2002; Beach et al. 2006; Environment Canada and Health Canada 2012). The estimated half-lives for PFOS (as the potassium salt) are >41 years in water (ATSDR 2009) and 114 days in the atmosphere (Brooke et al. 2004). The indirect half-life of PFOS was estimated (using an iron oxide photoinitiator model) to be ≥3.7 years (OECD 2002; Beach et al. 2006). Studies have not demonstrated the biodegradation of PFOS under aerobic or anaerobic conditions (Beach et al. 2006) and PFOS is considered to be resistant to microbial degradation (Health Canada 2006). Moreover, the abiotic degradation of certain PFOS precursor molecules can lead to PFOS as the end stage metabolite product (Martin et al. 2010). Hydrolysis rates (varying from days to weeks) for PFOS precursors are provided in 3M Company studies (Mendel 1977; 3M Company 1996; Hatfield 1999).

The information below is reproduced from Sanexen 2015.

PFAS present in ambient air return to earth via wet and dry depositions which may vary depending on regional atmospheric processes (Strynar et al. 2012). According to Strynar et al. (2012), soil likely plays an important role as a global sink. Indeed, the authors estimated that approximately 6% of the total production of PFOS is distributed globally in surface soils (estimation based on a median PFOS concentration in surface soil of 0.472 ng/g) (Strynar et al. 2012).

The application of biosolids is another source of PFAS, including PFOS to soils that would otherwise have lower inputs of these substances.

5.0 HEALTH EFFECTS

The information in this section, including subsections 5.1 to 5.5, is reproduced from Health Canada 2016.

Many studies have been conducted to investigate the effects of PFOS on health. The summary of literature on health effects for PFOS is based on a comprehensive review conducted by Sanexen Environmental Services Inc. 2013), and includes only the studies of direct relevance to the derivation of the health-based value.

5.1 Effects in Humans

5.1.1 Acute Toxicity

No epidemiological data regarding acute or short-term toxicity of PFOS were located.

5.1.2 Subchronic and Chronic Toxicity

Many quality epidemiological studies have been conducted. Large cohorts of workers and environmentally exposed populations have been followed, with observations of significant relationships between exposure to PFOS and lipid levels, liver and thyroid functions, and reproductive (fecundity, age of puberty, and sperm quality), immunological, and developmental (birth weight) outcomes. Although all of these studies present limitations to some extent, including in terms of study design, bias and confounders, the human weight of evidence provides a strong argument in favour of detrimental health effects of the compound. This information should support the choice of a health endpoint; however, deriving a safe exposure dose based on studies in humans remains a challenge because of the difficulty in characterizing a dose–response pattern with current studies. The use of epidemiological studies in the present assessment is important to verify the relevance of animal to human extrapolation, and the monitoring of future studies will help in determining the accuracy of the observed associations.

Most environmental studies among PFAA-exposed populations were conducted in the Mid-Ohio Valley within the C8 Science Project. The C8 Science Panel was convened as a result of a class action settlement against DuPont, and is composed of independent epidemiologists jointly selected by lawyers for the community and DuPont. The C8 Health Project is the largest study of a population exposed to PFAA in drinking water, containing residents of Ohio and West Virginia communities surrounding the DuPont Washington Works plant. The health survey was conducted in 2005–2006 on approximately 69,000 individuals, including children and adults. The main PFAA exposures in the community were to PFOA—the median PFOS serum concentrations in this population were 20.2 ng/mL, compared to 17.5 ng/mL in the general American population during the same period (Frisbee et al. 2009). Some longitudinal/prospective studies were also conducted among this population after a follow-up period. Some recent data in the project have not yet been published in peer reviewed literature; summaries of these studies—as well as panel conclusions and further information on the members of the panel—are available on the C8 Science Panel website (www.c8sciencepanel.org/panel.html).

5.1.2.1 Liver Effects

Some level of association between exposure to PFOS and alteration in liver enzymes has been observed, but no clear trend has been defined. A cross-sectional study found no association between PFOS serum levels (range = 20–2,110 ng/mL) of 3M Cottage Grove employees (Minnesota) participating in the medical surveillance exam (70% of them eligible for the study) and hepatic parameters (data were not shown in the report; Olsen et al. 2003b). In another cross-sectional study, a small linear association between levels of PFOS and of Alanine transaminase (ALT) was reported in participants of the C8 project (Gallo et al. 2012). However, the clinical significance of the low magnitude in ALT increase is unknown. An occupational study compared hepatic enzymes before and after the demolition of manufacturing facilities. A significant association was found between PFOS and decreased ALT among workers with baseline PFOS levels similar

to the general population. No association was found between PFOS and total bilirubin, AP or AST (Olsen et al. 2012). Overall, no definitive conclusion on liver toxicity can be drawn due to study limitations and low magnitude of enzymatic changes.

5.1.2.2 Immune Suppression

Studies in environmentally-exposed populations have identified associations between PFOS levels and decreased antibodies against various illnesses, but the influence of PFOS exposure on clinical immunosuppression (i.e., incidence of illnesses) appears to be more tenuous. A study in children found an inverse relationship in immune response with PFAA exposure (Grandjean et al. 2012; Grandjean and Budtz-Jørgensen 2013), with maternal cord PFOS levels negatively correlated with anti-diphtheria antibody concentration at 5 years. Moreover, children in this population demonstrated increased odds of not reaching protective antibody levels for diphtheria after vaccination at 7 years old (Grandjean et al. 2012). The prospective nature, sample size, low risk of selection bias and defined objectives make the results relevant to the studied population; however, relevance to other populations is questionable, as increased exposure to other potential immunosuppresants occurring in this region (Faroe Islands) was not accounted for in the study. Increased PFOS exposure was also associated with decreased antibodies against rubella in children from a prospective birth cohort of pregnant women from Norway (2007–2008; Granum et al. 2013). In contrast, prenatal exposure to PFOS was not associated with hospitalizations for infections in a Danish Cohort (1996–2002; Fei et al. 2010a), nor with episodes of common cold, gastroenteritis, eczema or asthma in the aforementioned Norwegian cohort (Granum et al. 2013). In a Taiwanese cohort study, the median serum PFOS concentration was significantly higher in asthmatic children (Dong et al. 2013), and prenatal exposure to PFOS was positively correlated with cord blood IgE levels, particularly in male children; however, there was no association with atopic dermatitis (Wang et al. 2011b). Cord blood IgE levels, food allergy, eczema, wheezing, or otitis media were not associated with maternal PFOS in female infants in a prospective cohort study of pregnant women from 2002 to 2005 in Japan (Okada et al. 2012).

Although some effects on the antibody response have been observed, conflicting results were common in the dataset, which remains relatively small. A low level of consistency was observed across studies, with variations between genders, specific microbial immunoglobins, infections, mother vs. child exposure, and child years, amongst other characteristics. Moreover, the risk of residual confounding, bias, and chance cannot be discarded. These flaws impede concluding on a causative mechanism, and the nature of the association remains unclear.

5.1.2.3 Lipidemia

Significant associations between PFOS and increased total cholesterol and alteration of other lipid parameters have been reported. A cross-sectional study found no association between PFOS serum levels (range 20–2,110 ng/mL) of 3M Cottage Grove employees (Minnesota) participating in the medical surveillance exam (70% of them eligible for the study) and lipid parameters (data were not shown in the report) (Olsen et al. 2003b). Careful interpretation is required because the data for these results were not published. A longitudinal study conducted in workers involved in the demolition of perfluoroalkyl manufacturing facilities found no clear association between PFOS levels and serum lipids, although some level of association was found between PFOS and increased HDL (Olsen et al. 2012). Some limitations include the self-reporting of employees' characteristics, low participation rate, the possibility of exposure to other contaminants, and relatively short follow-up times. In contrast, an unpublished cross-sectional study found lower HDL values in male employees with the highest serum PFOS levels. Another longitudinal study conducted in 560 adults (2005–2006 with follow-up in 2010) found a decrease in low-density lipoprotein (LDL) and total cholesterol with decreased serum PFOS level (no changes for HDL or TG) (Fitz-Simon et al. 2013). The clinical significance is uncertain, given the low number of participants changing from the high to the normal level of cholesterol categories, the unknown mechanism of action, and the low magnitude of the changes. Cross-sectional studies within the C8 Health Project found increasing trends for total cholesterol,

LDL, triglycerides, and the total cholesterol (TC)/HDL ratio with increasing PFOS (Steenland et al. 2009; Frisbee et al. 2010). A cross-sectional study of the general U.S. population indicated that adults in the highest serum PFOS quartile had higher TC levels than those in the lowest quartile (no association for serum LDL) (Nelson et al. 2010). In another cross-sectional study conducted in Inuits from Nunavik, a negative association was found between plasma PFOS level and triglycerides and the total cholesterol/HDL ratio, and a positive association was found with HDL levels (Château-Degat et al. 2010). The clinical relevance of very small alterations in cholesterol levels is unclear. Increased PFOS exposure also resulted in increased uric acid in two occupational and one general population studies (reviewed by Steenland et al. 2010). Overall, associations between PFOS and alterations in lipid parameters have been observed; however, the conclusions are limited by the lack of consistency across studies, the study designs, the possibility of selection bias, and chance finding from the high number of testing conducted.

5.1.2.4 Thyroid Disruption

Inconsistent effects on thyroid hormone levels were observed in PFOS-exposed populations. A cross-sectional study found no association between PFOS serum levels (range 20–2,110 ng/mL) of 3M Cottage Grove employees (Minnesota) participating in the medical surveillance exam (70% of them eligible for the study) and thyroid parameters (data were not shown in the report) (Olsen et al. 2003b). A cross-sectional study of the general population (C8 Health Project) indicated that PFOS was associated with an increase of serum total T4 (TT4) and a decrease of T3 uptake in both genders (Knox et al. 2011a). The association with PFOS and serum TT4 and T3 uptake was stronger in women, but lower than men for serum albumin. Another cross-sectional study conducted in the children enrolled in the C8 Health Project indicated a positive association between serum PFOS levels and increased TT4 levels (Lopez-Espinosa et al. 2012). Serum PFOS levels were not associated with prevalence of thyroid disease in a cross-sectional analysis of the general US population (Melzer et al. 2010). However, men from the highest serum PFOS quartile were more likely to report current (treated) thyroid disease. A cross-sectional study conducted in the Inuit population of Nunavik found negative associations between serum PFOS and serum TSH, T3, and thyroxin-binding globulin, and a positive association between serum PFOS and serum free T4 (fT4) (Dallaire et al. 2009). A matched-case control study found no association between environmental exposure to PFOS and hypothyroidism (TSH and fT4 levels) in pregnant women from Edmonton, Canada (Chan et al. 2011). A negative correlation was found between PFOS levels in fetal and maternal serum and T3 in the general population in South Korea (Kim et al. 2011a). No association was found between PFOS and TSH in a small population of anglers in New York (Bloom et al. 2010).

Although associations between serum PFOS and TT4, fT4, T3 and TSH were observed, no clear trend for thyroid hormone changes related to PFOS exposure can be established because results were equivocal, it was not possible to calculate cumulative exposure, individuals with thyroid diseases were excluded, possibly biasing the results, and temporality cannot be established with the cross-sectional study design.

5.1.2.5 Kidney Effects

An increased risk of chronic kidney disease (reduced estimated glomerular filtration rate) was reported in a cross-sectional study of the general US population (Shankar et al. 2011). Causality will be difficult to be established for adverse kidney effects, as altered kidney function could cause an increase in serum PFOS levels.

5.1.3 Carcinogenicity

Some associations between PFOS and risk of cancer of the bladder, breast, male reproductive organs, and overall cancers were observed; however, the evidence does not support the carcinogenicity of PFOS. In an occupational study, PFAA workers (n = 2,083) were found to have an elevated risk for bladder cancer mortality in the City of Decatur, Alabama (Alexander et al. 2003). However, the authors reported that it was

difficult to draw any definite conclusions because there were only 3 cases of bladder cancer and the workers were exposed to several compounds concurrently (all 3 cases were production workers considered at high PFOS exposure, and had also worked at the plant incinerator or wastewater treatment plant). Moreover, no adjustment was conducted for race, smoking or other contaminants; the exposure was based on job categories; the cases with bladder cancer were not the ones with the highest exposure; and there was a risk of selection bias, lowering the credibility of the results. In a follow-up study, there was no association between PFOS exposure and an increased risk of bladder cancer (Alexander and Olsen 2007). In an earlier analysis of the same cohort, the risks for episodes of medical care for overall and male reproductive cancers were greatest in the group of employees with the highest and longest exposures to fluorochemicals (Olsen et al. 2001). A prospective cohort study was conducted in the general population of Denmark to investigate the possible association between PFOS exposure and cancer risk (Eriksen et al. 2009). No significant correlation was found between PFOS serum concentrations and the incidence of prostate, bladder, pancreas and liver cancer across quartiles of serum PFOS. Evidence of a relationship between PFOS and breast cancer was found in a small case–control study conducted in Greenlandic Inuit women. However, considering that the risk of breast cancer was increased in relation with several chemicals, confounding by other compounds or chemical groups may have played a role in the observed association (Bonefeld-Jorgensen et al. 2011).

Although some evidence of an association between PFOS and the risk of cancer has been observed, the effects were equivocal, and no clear trend could be determined due to limitations in the studies (small number of cases, confounding, and participant selection bias).

5.1.4 Developmental and Reproductive Toxicity

Recent epidemiological studies have observed effects on birth weight, developmental milestones, thyroid hormones, immune system, fecundity, and age of puberty, indicating that the fetus, neonate and young children may be considered as vulnerable sub-populations to prenatal and early life PFOS exposure (Apelberg et al. 2007; Stein et al. 2009; Washino et al. 2009; Andersen et al. 2010; Hoffman et al. 2010; Gump et al. 2011; Stein and Savitz 2011; Maisonet et al. 2012).

5.1.4.1 Developmental Toxicity

Inverse associations between PFOS at early pregnancy and birth weight have been reported in different general population studies. A cross-sectional study conducted by the C8 Science Panel found an association between serum PFOS levels and low birth weight at PFOS levels above the median (Stein et al. 2009). Lower birth weight and higher weight at 20 months were observed in girls born from mothers with higher prenatal concentration of PFOS (who were previously selected for a nested case-control study of pubertal development among mothers enrolled in the Avon Longitudinal study of Parents and Children in Great Britain [ALSPAC]) (Maisonet et al. 2012). However, the results were of poor precision (–140 g, 95% CI: –238 to –42). Also, the analysis of a prospective cohort study in Japan (n = 230) indicated that birth weight of female neonates was negatively correlated with prenatal exposure to PFOS after adjustment for multiple covariates (Washino et al. 2009). Again, the results were of poor precision due to high variability in the dataset (infants were estimated to be 269 g lighter, with 95% CI ranging from 73 to 466), low participation rate (29%), and the possibility of measurement errors (as suggested by the authors). Small but significant negative associations were observed with head circumference, ponderal index, and birth weight in a cross-sectional study of the general population in Baltimore, Maryland (Apelberg et al. 2007). In contrast, no association between maternal levels of PFOS and any of the measured fetal growth indicators (placental weight, birth length and head and abdominal circumferences) was found in a random sample of women and their offspring in the Danish National Birth Cohort (Fei et al. 2008b). Other general population studies in Canada and Denmark found no associations between maternal serum PFOS levels and birth weight (Fei et al. 2007; Monroy et al. 2008; Hamm et al. 2010). PFAA (including PFOS) were not associated with BMI and waist circumference in a

prospective cohort study with long-term follow-up (20 years) among pregnant women recruited within the Danish National Birth Cohort and their male or female children (Halldorsson et al. 2012).

PFOS-induced developmental health effects on thyroid and neurobehaviour have also been investigated. A negative correlation between maternal serum PFOS levels and fetal T3 levels was found in a small South Korean cross-sectional study (but not with TSH and TT4 levels or with birth weight) (Kim et al. 2011a). In the US general population, a higher risk of parental report of diagnosis of attention deficit/hyperactivity disorder (ADHD) with higher levels of PFOS was found in children aged 12–15 years (Hoffman et al. 2010). In a cross-sectional study conducted within the C8 Health Project, no association was found between PFOS and the prevalence of parents who reported that a doctor diagnosed their child with ADHD or a teacher told them their child had a learning disorder (Stein and Savitz 2011). No association was found between maternal serum PFOS and motor or developmental milestones (fine/gross motor, attention, cognition and language) in children aged 18 months (Fei et al. 2008a), or behavioral or motor coordination problems in children aged 7 years old (Fei and Olsen 2011).

Although some effects on development have been observed in population studies, the evidence supporting a link between early-life exposure to PFOS and developmental toxicity is equivocal because most studies were not designed to allow causal inference. The most preocupying evidence come from the prospective studies showing an increased risk of altered birth weight in Britain and Japan; however, the clinical significance of these findings is unclear, and other larger studies would be needed to support the results considering the poor precision of the point estimate, the relatively small size of the studies and the risk of confounding and bias.

5.1.4.2 Reproductive Toxicity

The main findings suggest a possible link between PFOS exposure and reduced fecundity in cohort and case–control studies and delayed puberty; however, the quality of the evidence is limited and not sufficient to define the nature of the relationship.

A delay in the median age of puberty in both sexes was associated with PFOS concentrations in a cross-sectional study of individuals aged 8–18 years within the C8 Health Project (Lopez-Espinosa et al. 2011). The authors questioned the clinical significance of the results because the median age at puberty in this study was similar to the median age reported in the general U.S. population (12.5 vs 12.9 years), and the mechanisms behind the delayed onset of puberty are unclear. PFOS exposure in utero was found to be slightly (but not significantly) associated with an increased odds of earlier puberty in girls participating in the aforementioned ALSPAC cohort (Christensen et al. 2011). The authors mentioned the results could be biased by the misclassification of exposure and selection of participants.

The influence of PFOS exposures on sperm parameter observations is inconsistent. Serum levels of PFOS were associated with a decreased number of normal sperm in young Danish men aged 18.2–25.2 years in a cross-sectional study (Joensen et al. 2009). A tendency toward reduced levels of all semen parameters (testosterone, free androgen, etc.) was also found in the highest quartile. However, there was a high risk of selection bias and chance findings. A positive association between serum PFOS and a lower proportion of morphologically normal sperm of pregnant partners was identified in the combined groups of three populations from Greenland, Poland, and Ukraine (Toft et al. 2012). A few significant associations with sperm concentration and total sperm count were found in the analyses based on single countries; however, there was no overall dose-response, the results are subject to the ecological fallacy, and the authors mentioned the results were likely due to chance findings. In a cross-sectional study conducted in men from Durham, NC, a positive correlation between plasma PFOS and serum LH levels was found, but there was no association with altered semen quality (Raymer et al. 2012). Maternal PFOS at pregnancy week 30 (in utero exposure) was not associated with sperm quality and serum reproductive hormones in male offspring at age 19–21 years in a pregnancy cohort in Denmark (Vested et al. 2013). In conclusion, no clear pattern of association between

maternal PFOS levels and sperm quality can be established because of studies' inconsistencies, design limitations, and high risk of selection bias.

An association between PFOS exposure and a reduction in fecundity has been observed; however, the studies were not robust and the results are inconclusive. A reduction in fecundity (increased time to pregnancy and irregular menstrual periods) was found to be associated with the plasma PFOS levels in 1,240 parous/nulliparous women from the Danish National Birth Cohort; however, the information for multiple confounders was omitted from the analysis (sperm quality, frequency of intercourse, etc.) (Fei et al. 2009). Increased relative odds of subfecundity (time to pregnancy greater than 12 months) was also reported in a case–control study on parous women enrolled in the Norwegian Mother and Child Cohort Study (no association in nulliparous women) (Whitworth et al. 2012). The lack of adjustment for confounders generates doubt on the validity of their observation. No association between serum PFOS and time to pregnancy or fecundity was found in nulliparous women in a longitudinal cohort study in Denmark (Vestergaard et al. 2012). In an Italian case–control study, couples affected by infertility tend to have higher PFOS levels and to have a higher gene expression of nuclear receptors involved in steroid and xenobiotics metabolism; however, the mechanism of action remains unclear (La Rocca et al. 2012).

The occurrence of self-reported preeclampsia in the Mid-Ohio Valley was associated with PFOS for exposure above the median; however, the results were of poor precision (Stein et al. 2009). A significant inverse association was found between PFOS and serum estradiol levels in perimenopausal and menopausal age groups of women from the C8 Health Project; however, temporality cannot be established with the study design (Knox et al. 2011b).

A prospective cohort study recruited 1,400 pregnant women (randomly out of 43,045) within the Danish National Birth Cohort (DNBC, 1988–1989) and measured PFOS concentration in their plasma (Fei et al. 2010b). Duration of breastfeeding was reported 6 and 18 months after birth by phone interviews. The risk of breastfeeding for a shorter period was higher with increasing plasma PFOS concentrations. For example, the risk (adjusted hazard ratio) of shorter breastfeeding duration (weeks) for women with plasma PFOS > 43.3 ng/mL was 1.4 (95% CI 1.2-1.6) times higher than for those with plasma PFOS 6.4-26.6 ng/mL, after adjusting for maternal age at delivery, pre-pregnancy BMI, maternal socioeconomic status, alcohol consumption and smoking (the trend for an increase in risk with increasing four-quartile comparison was also significant). Also, the odds (adjusted odds ratio) of weaning before 6 months of age was 1.20 (95% CI: 1.1–1.4) times higher for each 10 ng/mL increase in plasma PFOS when restricting the model to multiparous women (not significant in primiparous women), after statistical adjustments. A similar association was observed with weaning before 3 months of age. However, more studies would be needed to support these results, since PFOS plasma concentration was measured only one time, only 18% of eligible women participated in the DNBC study, there is a risk of outcome recall bias (mothers might not report accurately the date of weaning), and the authors did not rule out the possibility that reverse causation could explain the association (considering that women that have breastfed longer can be more likely to breastfed longer their next infants, and that PFOS is excreted in breast-milk, lowering the plasma concentration).

Correlations and associations have been observed between PFOS and altered birth weight, fecundity, fertility, sperm quality, preeclampsia, shorter duration of breastfeeding, and thyroid hormones. However, the evidence remains insufficient to clarify the nature of the relationship due to the lack of consistency across studies, important limitations in study design, and risk of bias and confounding.

5.2 Effects on Experimental Animals

The vast majority of animal studies stated that PFOS exposure was performed using the potassium salt of PFOS (K+PFOS), with the exception of studies by Qazi et al. which used the tetraethylammonium salt (Qazi et al. 2010b) or tetrabutylammonium salt (Qazi et al. 2009b, 2010a) of PFOS. Studies that did not state the specific salt used in their study were assumed to have used the potassium salt, as this was the most common

compound used. Most of the studies did not state whether the administered dose referred to the K+PFOS compound, or specifically to the PFOS ion; only one study (Peden-Adams et al. 2008) stated that the doses reflect the concentration of PFOS ion, separate from the potassium salt. The summaries described herein use the concentrations and doses stated by authors. This approach is also used for quantitative assessments; however, as the PFOS ion contributes to 93% of the molar weight of K^+PFOS and is released from the compound upon exposure, only minor quantitative differences would result from using K^+PFOS and PFOS doses interchangeably.

5.2.1 Acute Toxicity

A mean oral LD50 value of 251 mg/kg bw was calculated for male and female CD rats based on a single administration of PFOS (100–1,000 mg/kg bw) by gavage (5/sex/group) (Dean and Jessup 1978). An inhalation LC_{50} of 5,200 mg/m^3 was determined in Sprague-Dawley rats (5/sex/group) exposed to PFOS dust in air (1,890–45,970 mg/m^3) for one hour (Bio/Dynamics 1979; Rusch 1979;).

Single oral exposure of rodents (rats and mice) to PFOS at ≥250 mg/kg bw was shown to cause tonic convulsions when ultrasonic stimulus was applied to the animals (Sato et al. 2009). PFOS alone did not cause neurotoxic symptoms, morphological changes or physiological alteration (hormone concentration). Although the convulsive effect was observed at very high doses, it is considered as neurotoxicity induced by PFOS because the same ultrasonic stimulus did not cause convulsions in control animals or in animals treated with PFOA.

Skin irritation was not observed in albino New Zealand White rabbits dermally exposed to PFOS (Biesemeier and Harris 1974; as cited in Health Canada 2016). Severe eye irritation was reported in rabbits (0.1 mL ocular application, washout after 5 or 30 seconds) (Riker Laboratories Inc. 1981). Additional studies reported mild to moderate eye irritation after ocular PFOS exposure (Biesemeier and Harris 1974; Warf Institute Inc. 1975; Hazleton Laboratories America Inc. 1987; Hazleton Wisconsin Inc. 1994; Corning Hazleton Inc. 1997). Acute developmental neurobehaviour studies are discussed in Section 5.2.5.

5.2.2 Short-term Exposure

Studies documenting the toxicity of PFOS after short-term oral exposure identified four main targets, namely the immune system, the liver, serum lipids and thyroid. The immune system appears to be the most sensitive target, with a LOAEL of 0.00166 mg/kg bw per day and a NOAEL of 0.000166 mg/kg bw per day in mice (Peden-Adams et al. 2008). The lowest LOAELs for hepatic, lipid, and thyroid effects were 0.024 mg/kg bw per day (Butenhoff et al. 2012b), 0.03 mg/kg bw per day (Seacat et al. 2002), and 0.15 mg/kg bw per day (Seacat et al. 2002), respectively. This section will focus primarily on these key effects observed at the lowest levels, and will only briefly discuss other types of changes observed in animals.

5.2.2.1 Immune System Effects

Immune system effects observed at the lowest levels tend to indicate that immunosuppression is the effect of greatest concern. Studies designed to identify the effects of PFOS on the immune system measured mortality from infection, changes in levels of immunoglobulins and cytokines, activity levels of immune cells, and lymphocyte phenotype and proliferation. In studies that were not designed to specifically study immunological effects (i.e., higher dose bioassays), more general immune system toxicity was measured as decreases in white blood cell counts, and organ weight and histological changes in the spleen and thymus. The various immune system effects were reported only in mice and rats, with no immunotoxicity studies designed for other species.

The IPCS (2012) has presented a continuum of the strength of evidence provided for various types of data that could suggest the occurrence of immunosuppression. In animal studies, host resistance data and immune function data (including antibody production and NK cell function) provide the strongest weight of evidence for immunotoxicity. Data from observational immune assays (including lymphocyte phenotype and

proliferation, and changes in cytokine levels), as well as evidence of changes in haematology and organ histopathology and weight, are all classified as providing equivocal evidence of immunosuppression. This section will discuss the effects in order from strongest to weakest weight of evidence for immunosuppression. Because several studies for PFOS provide evidence of decreased host resistance and immune function, these studies will form the greater focus of this section.

Only one study investigated the effect of PFOS on host resistance (i.e., the top tier in the IPCS framework) to infections. In the study, female B6C3F1 mice were exposed to PFOS at gavage doses of 0, 0.005 or 0.025 mg/kg bw per day for 21 days, and subsequently innoculated with Influenza A virus (Guruge et al. 2009). Increased mortality from Influenza A infection was observed in mice exposed to 0.025 mg/kg bw per day. Although B6C3F1 appears to be a strain of mice that is sensitive to PFOS effects, female mice have been demonstrated to be less sensitive than males to other immune outcomes arising from PFOS exposure.

The most sensitive effect observed in animal studies in the IPCS category of immune function data was the suppression of T-dependent antigen response (TDAR) for IgM, using sheep red blood cell (SRBC) as an antigen. The lowest LOAEL on this effect was 0.00166 mg/kg bw per day (NOAEL of 0.000166 mg/kg bw per day; Peden-Adams et al. 2008), and decreases tended to have clear dose dependence in most studies. The effect was observed at the lowest levels in adult mice in three studies described below:

- At ≥0.00166 mg/kg bw per day in male and ≥0.0166 mg/kg bw per day in female B6C3F1 mice (n = 5/dose) exposed through oral gavage (doses of K^+PFOS: 0, 0.000166, 0.00166, 0.00331, 0.0166, 0.0331 or 0.166 mg/kg bw per day) for 28 days (Peden-Adams et al. 2008).
- At ≥0.083 mg/kg bw per day in male C57BL/6 mice (n = 10/dose) exposed by oral gavage (to doses of 0, 0.00833, 0.0833, 0.417, 0.833, and 2.083 mg/kg bw per day) for 60 days (Dong et al. 2009).
- At ≥0.083 mg/kg bw per day in male C57BL/6 mice (n = 6/dose) exposed by oral gavage (to doses of 0, 0.00833, 0.0167, 0.0833, 0.417, and 0.833 mg/kg bw per day) for 60 days (Dong et al. 2011).

SRBC-specific IgM decreases were also observed at 5 mg/kg bw per day (but not 1 mg/kg bw per day) in male B6C3F1 mice exposed prenatally to PFOS on GD 1–17 (Keil et al. 2008). Moreover, decreases in non-specific serum IgM were observed at ≥5 mg/kg bw per day in male C57BL/6 mice exposed to 5 or 20 mg/kg bw per day for 7 days (Zheng et al. 2011).

In contrast, a study exposing male C57BL/6 mice to 0.25 mg/kg bw per day (as the tetraethylammonium salt of PFOS; no other dose levels were used in the study) for 28 days did not find any change in serum levels of anti-SRBC or anti-TNP–LPS IgM, nor in the number of splenic cells secreting anti-SRBC IgM (Qazi et al. 2010b).

PFOS-induced changes in serum levels of other immunoglobulins—which also fall under the IPCS category of immune function data—were observed at higher exposure levels. In contrast with IgM levels, IgG and IgE levels tended to be increased after PFOS exposure. In male C57BL/6 mice, increased SRBC-specific IgE and IgG were observed at the highest dose (0.833 mg/kg bw per day; see more detailed study description above) (Dong et al. 2011). Increases in non-specific serum total IgG were observed at 5 mg/kg bw per day—but not 20 mg/kg bw per day—in male C57BL/6 mice exposed to PFOS for 7 days (Zheng et al. 2011). A study of male rats exposed to 0.14–6.34 mg/kg bw per day (Lefebvre et al. 2008) explored the effects of PFOS on various IgG subtypes; the study found a significant trend for increased total serum IgG2a and IgG2c and secondary T-dependent IgG response (using KLH as an antigen). Total serum IgG1 was decreased in male rats exposed only to the two lowest doses (0.14 and 1.33 mg/kg bw per day).

The final effect in the IPCS category of immune function data was altered splenic natural killer (NK) cell activity, which was observed to be altered in mice in studies previously described above; activity tended to be increased at the lowest doses and decreased at higher doses. Decreased splenic NK cell activity was

observed in male B6C3F1 mice exposed to 0.0166–0.166 mg/kg bw per day (Peden-Adams et al. 2008). In Dong et al. (2009), non-monotonic changes in the activity were observed in male C57BL/6 mice, with increases at 0.083 mg/kg bw per day, no effects at 0.417 mg/kg bw per day, and decreases at 0.833 and 2.083 mg/kg bw per day. Splenic NK cell activity was decreased in male mice exposed prenatally to ≥1 mg/kg bw per day (Keil et al. 2008) and adult male mice exposed to ≥20 mg/kg bw per day for 7 days (Zheng et al. 2009). In female mice, no changes in activity were observed at doses up to 0.166 mg/kg bw per day (Peden-Adams et al. 2008), but decreased NK cell activity was observed in those exposed prenatally to 5 mg/kg bw per day (Keil et al. 2008).

Additional immunological effects observed in studies of PFOS exposure were described by IPCS as types of data that provide only equivocal evidence of immunosuppression. Although the data support the PFOS-induced immune suppression described above, they are described only briefly as they are not robust enough to be used as a basis for a drinking water quality guideline. The observed effects were as follows (with IPCS classifications indicated in brackets):

- Alterations in subpopulations of B-cell, T-cell, and presenting antigen cells in the spleen and thymus in male and female mice, with a lowest LOAEL of 0.00331 mg/kg bw per day (Keil et al. 2008; Peden-Adams et al. 2008; Dong et al. 2009; Qazi et al. 2009b; Zheng et al. 2009). No effects on blood lymphocyte phenotype were observed in rats exposed to ≤7.58 mg/kg bw per day (Lefebvre et al. 2008) [observational immune assays].
- Alterations in levels of various cytokines in male and female mice, with a lowest LOAEL of 0.0031 mg/kg bw per day (Qazi et al. 2010a; Dong et al. 2011, 2012b; Fair et al. 2011; Mollenhauer et al. 2011; Zheng et al. 2011). The nature of effects was described by Zheng et al. (2011) and Dong et al. (2011) as appearing to create an excessive Type 1 response and deficient Type 2 response (i.e. a predominance in humoral immunity and deficiency in cell-mediated immunity, which can lead to a decreased ability to fight intracellular pathogens and cancerous cells [Guruge et al. 2009; Zheng et al. 2011]) [observational immune assays].
- Decreased cellularity and lymphocyte proliferation in male mice, with a lowest LOAEL of 0.417 mg/kg bw per day (Dong et al. 2009, 2012b; Qazi et al. 2009b) [observational immune assays].
- Reduced leukocyte counts in rats at ≥6 mg/kg bw per day (Goldenthal et al. 1978a) [haematological data].
- Evidence of increased apoptosis in spleen and thymus, at ≥0.0833 mg/kg bw per day in mice (Wang et al. 2011b; Dong et al. 2012a; Zhang et al. 2013) and ≥3.21 mg/kg bw per day in rats (Lefebvre et al. 2008) [histopathological data].
- Histological effects in thymus and spleen at ≥5 mg/kg bw per day in mice (Qazi et al. 2009b; Wang et al. 2011b; Zhang et al. 2013) and ≥18 mg/kg bw per day in rats (Goldenthal et al. 1978a; Cui et al. 2009) [histopathological data].
- Decreased absolute and/or relative weight of thymus and spleen at ≥0.417 mg/kg bw per day in male mice (Dong et al. 2009, 2012a; Qazi et al. 2009b; Zheng et al. 2009, 2011) and at 0.984 mg/kg bw per day in male rats (Butenhoff et al. 2012b) [organ weight data].
- Increased serum corticosterone in male mice at 0.25 mg/kg bw per day (Qazi et al. 2010b) and ≥20 mg/kg bw per day (Zheng et al. 2009, 2011), but not at ≤0.833 mg/kg bw per day (Dong et al. 2011) [not classified by IPCS, but supportive data].

Sensitivity to immunological effects appears to be dependent on several factors. The influence of species on effects is difficult to ascertain, as only one rat study was specifically designed to measure immune effects (Lefebvre et al. 2008); however, the NOAEL in the study was several orders of magnitude higher than some of the LOAELs from mouse studies (Peden-Adams et al. 2008; Dong et al. 2009, 2011;). Even within a single species, differences in sensitivity might occur among strains—effects on SRBC-specific IgM levels and splenic NK cell activity have been observed at lower levels in B6C3F1 mice (Peden-Adams et al. 2008) than in C57BL/6 mice (Dong et al. 2009, 2011), even after a shorter duration of exposure (28 days vs. 60 days). Moreover, these effects were observed at lower levels in males than in females (Peden-Adams et al. 2008). However, there are no indications that pre-natally exposed mice are more sensitive to immunological effects than adults, as changes in SRBC-specific IgM response and splenic NK cell activity were not observed at ≤1 mg/kg bw per day in male mice exposed in utero on GD 1–17 (Keil et al. 2008), whereas LOAELs for these effects were <0.1 mg/kg bw per day in adult mice (Peden-Adams et al. 2008; Dong et al. 2009, 2011).

5.2.2.2 Hepatic Effects

The hepatic effects occurring at the lowest levels in short-term studies were increases in liver weight. Histological changes in the liver and increases in serum enzymes that are indicators of adverse hepatic effects were also observed at higher levels.

Increased liver weight (absolute or relative) was observed in studies of varying durations, with lowest LOAELs at:

- 0.0833 mg/kg bw per day in C57BL/6 mice (10/dose) exposed via gavage for 60 days to 0.00833, 0.0833, 0.417, 0.833, and 2.083 mg/kg bw per day (Dong et al. 2009). The effect was also observed at higher doses in many other mouse studies (Thibodeaux et al. 2003; Yahia et al. 2008; Era et al. 2009; Qazi et al. 2009b, 2010a, 2010b; Zheng et al. 2009, 2011; Dong et al. 2011, 2012a; Wan et al. 2011; Wang et al. 2011b; Zhang et al. 2013). Conversely, no increase in liver weight was observed in mice exposed up to 0.166 mg/kg bw per day for 28 days (Fair et al. 2011), 10 mg/kg bw per day for 7 days (Wan et al. 2011), or 10.5 mg/kg bw per day for 4 days (Abbott et al. 2009).
- 0.15 mg/kg bw per day in female and 1.33 mg/kg bw per day in male Sprague-Dawley rats (15/group) with exposure to 2, 20, 50, or 100 ppm PFOS in feed (0.14, 1.33, 3.21, and 6.34 mg/kg bw per day in males and 0.15, 1.43, 3.73, and 7.58 mg/kg bw per day in females) for 28 days (Lefebvre et al. 2008). The effect was also observed at higher doses in many other rat studies (Goldenthal et al. 1978a; NOTOX 1999; Seacat et al. 2003; Thibodeaux et al. 2003; Cui et al. 2009; Yu et al. 2009a; Elcombe et al. 2012a).
- 0.75 mg/kg bw per day in monkeys (n=6) with exposure to 0.03, 0.15, and 0.75 mg/kg bw per day by oral bolus dose (Seacat et al. 2002).

Increased fetal liver weight was also observed in developmental studies; this effect is described in Section 5.2.5.

Increases in histological effects were observed in short-term studies. The study in which the effects were observed at the lowest levels (Seacat et al. 2003) was of rats in 4- and 14-week early sacrifice groups of a 2-year dietary study (Butenhoff et al. 2012b; histological effects in the liver in this study are summarized in Section 5.2.3). The LOAELs in the 4-week study were 0.37 mg/kg bw per day in males and 1.77 mg/kg bw per day in females; in the 14-week study, the values were 0.34 mg/kg bw per day in males and 1.56 mg/kg bw per day in females. Hepatic hypertrophy and cytoplasmic vacuolation were observed in these dose groups. Similar effects were observed at higher doses in other rat studies (Elcombe et al. 2012a; Goldenthal et al. 1978a; NOTOX 1999; Cui et al. 2009), and in studies of monkeys (Seacat et al. 2002). Additional hepatic gross and histological effects observed at higher doses included:

- Brown liver in male rats exposed to 3.2 mg/kg bw per day (Christian et al. 1999)
- Fatty changes in male rats exposed to ≥5 mg/kg bw per day (Kim et al. 2011b), and
- Focal or flakelike necrosis at ≥5 mg/kg bw per day and focal hemorrhage, erythrocytic transudation, and focal hepatocytic degeneration accompanied by inflammatory cellular infiltration at 20 mg/kg bw per day in male rats (Cui et al. 2009).

Serum enzymes that are potential indicators of adverse liver effects were increased in several studies. ALT was increased in male rats exposed to 1.33 mg/kg bw per day for 14 weeks in diet (Seacat et al. 2003). Increased AST and ALT was also observed in rats exposed to 6 mg/kg bw per day (Goldenthal et al. 1978a). Conversely, no significant increases in serum ALT or AST were observed in rats exposed up to 9.65 mg/kg bw per day for 7 days (Elcombe et al. 2012a). Decreased serum bilirubin and increased serum bile acids were also observed in male monkeys exposed to 0.75 mg/kg bw per day (Seacat et al. 2002). Increased serum alkaline phosphatase was observed in male mice exposed to 0.005% PFOS in feed (approximately 6.5 mg/kg bw per day, using Health Canada's default assumption that 1 ppm in feed is equivalent to 0.13 mg/kg bw per day in mice [Health Canada 1994]) (Qazi et al. 2010a). A slight decrease in serum alkaline phosphatase was observed in male monkeys exposed to 0.5 mg/kg bw per day (but not 1.5 or 4.5 mg/kg bw per day) for 90 days (Goldenthal et al. 1978b).

5.2.2.3 Serum Lipid Effects

Decreased total cholesterol and HDL cholesterol were the serum lipid effects observed at the lowest levels in short-term studies; the various serum lipid measurements were decreased in monkeys, mice, and rats in the vast majority of studies that considered these endpoints. Decreased LDL and triglycerides were also measured in various studies. The lowest LOAEL for this endpoint was 0.03 mg/kg bw per day.

The LOAEL of 0.03 mg/kg bw per day for this endpoint was observed in a longer duration (26 week) study conducted in male and female Cynomolgus monkeys (4-6 animals per group) administered PFOS (0, 0.03, 0.15, or 0.75 mg/kg bw per day) by oral intubation of PFOS in a capsule (Seacat et al. 2002). Serum concentrations of cholesterol and triglycerides were measured before treatment and at several time points during treatment (Day 37, 62, 91, 153 and 182); HDL cholesterol was only analyzed on days 153 and 182. The changes considered consistent and statistically/biologically significant by the authors were decreased total cholesterol in both sexes at 0.75 mg/kg bw per day and decreased HDL (at 0.03 and 0.75 mg/kg bw per day in males, 0.15 and 0.75 mg/kg bw per day in females). At various time points following treatment at the lowest dose level (0.03 mg/kg bw per day), cholesterol levels were statistically significantly decreased compared to controls in male and female monkeys, and HDL levels were decreased in male monkeys, with no clear dose or time relationship. Lower levels of HDL (females) were observed at 0.15 mg/kg bw per day. Based on their statistical analyses, the investigators concluded that the NOAEL in this study was 0.15 mg/kg bw per day (LOAEL of 0.75 mg/kg bw per day) (Seacat et al. 2002).

However, both EFSA and Health Canada proposed different interpretations of the findings by Seacat et al. (2002). EFSA (2008) considered that the changes in HDL observed at this dose level were treatment-related and therefore concluded that it was justified to consider 0.03 mg/kg bw per day as a NOAEL (LOAEL of 0.15 mg/kg bw per day). Health Canada (2013c) considered that the statistical approach used in the original study (Seacat et al. 2002) was inadequate to interpret measures carried out repeatedly throughout the study and instead used linear mixed models to assess the effects of dose on these endpoints (TG, HDL, and cholesterol). Based on these models, Health Canada assessed the effect of dose and days on each endpoint and found a significant effect ($p=0.0003$ to $p<0.0001$) of dose on cholesterol and HDL in both sexes. There was no dose effect on the TG endpoint among both males and females, although when one outlier point for TG in males was removed, an overall significance between dose groups was observed ($p=0.0213$).

Differences between days were generally observed in all endpoints in both males and females. Results from Dunnett's pair wise test comparing treatment groups to control group indicate a statistically significant difference at ≥0.03 mg/kg bw per day for HDL in males, at ≥0.15 mg/kg bw per day for decreased cholesterol (females) and at 0.75 mg/kg bw per day for decreased cholesterol in males (for TG, only the lowest group was different from control when the outsider data point was removed). The time–dose interaction was significant for cholesterol in females (Health Canada, 2013c). Based on this statistical analysis, the LOAEL should be 0.03 mg/kg bw per day for decreased HDL in males (no NOAEL) and 0.15 mg/kg bw per day for decreased total cholesterol (NOAEL: 0.03 mg/kg bw per day).

The other monkey study for PFOS (Goldenthal et al. 1978b) also observed a significant reduction in serum cholesterol, at 4.5 mg/kg bw per day after 90 days of exposure. In a lower dose group (1.5 mg/kg bw per day), one of the female monkeys (i.e., half of the females in the dose group) had very low serum cholesterol.

Decreases in serum lipid parameters were also observed in other species. The LOAEL in mice was 0.166 mg/kg bw per day for total cholesterol in animals exposed for 28 days, with a NOAEL of 0.0331 mg/kg bw per day (Fair et al. 2011). Decreased triglycerides were observed at ≥5 mg/kg bw per day in mouse dams exposed to PFOS on GD 1–17 (Thibodeaux et al. 2003). Total cholesterol and triglycerides were also decreased in mice exposed to 0.005% PFOS in feed (sole treatment group; approximately 6.5 mg/kg bw per day, using Health Canada's default assumption that 1 ppm in feed is equivalent to 0.13 mg/kg bw per day in mice [Health Canada 1994]) (Qazi et al. 2010a).

In rats, the lowest LOAEL of 0.4 mg/kg bw per day was observed in dams exposed beginning 42 days prior to mating, until either gestational day 20 (for rats delivering by Caesarean section) or lactation day 4 (for rats delivering naturally; Luebker et al. 2005b). At this dose, total serum cholesterol was decreased; serum triglycerides were decreased only at ≥1.6 mg/kg bw per day. These effects were supported by decreased serum cholesterol (Seacat et al. 2003; Thibodeaux et al. 2003; Elcombe et al. 2012a) and decreased triglycerides (Thibodeaux et al. 2003; Elcombe et al. 2012a) in rats exposed to higher doses of PFOS.

Decreased liver cholesterol and triglycerides were also observed at the lowest dose in which this endpoint was studied (1.6 mg/kg bw per day, in rats dams in a developmental study; Luebker et al. 2005b).

5.2.2.4 Thyroid Effects

A LOAEL of 0.15 mg/kg bw per day for altered thyroid hormone levels was observed in male and female Cynomolgus monkeys (4–6 animals per group) administered potassium PFOS (0, 0.03, 0.15, or 0.75 mg/kg bw per day) for 26 weeks by oral intubation of PFOS in a capsule (Seacat et al. 2002). Serum concentrations of TSH and free and total T3 and T4 were measured before treatment and at several time points during treatment (Day 37, 62, 91, and 182). The thyroid hormone changes considered consistent and statistically/biologically significant by the authors were increased TSH and decreased TT3 in males and females at 0.75 mg/kg bw per day. At 0.15 mg/kg–bw per day, the changes observed included increased levels of TSH (males) and lower T3 concentrations (males and females). Some changes in T4 were also observed, but they were not consistent (including inconsistencies in direction). Based on the authors' statistical analysis, they stated that the LOAEL for thyroid hormone changes was 0.75 mg/kg bw per day (NOAEL = 0.15 mg/kg bw per day).

However, as was described for serum lipid effects, Health Canada & EFSA performed reinterpretations of the Seacat et al. (2002) results. EFSA considered that the changes in thyroid hormones observed at 0.15 mg/kg bw per day were treatment-related and therefore concluded that it was justified to consider 0.03 mg/kg bw per day as a NOAEL (LOAEL of 0.15 mg/kg bw per day) (EFSA 2008). Health Canada's reanalysis (2013c) was similar to that described for the serum lipid parameters (Section 5.2.2.3). Results from Dunnett's pair wise test comparing treatment groups to control group indicate a statistically significant difference at ≥0.15 mg/kg

bw per day for decreased TT3 (both sexes) and decreased TT4 (females only). The time–dose interaction was significant for T3, T4 and TSH in males and for T4 in females (Health Canada 2013c). Based on this statistical analysis, the LOAEL is considered to be 0.15 mg/kg bw per day for decreased TT3 and TT4 (NOAEL: 0.03 mg/kg bw per day).

The LOAEL for changes in thyroid hormones in rats was similar to that for monkeys. In a developmental study (Wang et al. 2011a), the effects were observed in rat dams exposed from GD 1 to PND 14 to 3.2 ppm of PFOS in feed (0.16 mg/kg bw per day using Health Canada's default assumption that 1 ppm in feed is equivalent to 0.05 mg/kg bw per day in rats [Health Canada 1994], an assumption that might not be relevant in pregnant rats). The LOAEL was for dose-dependent decreases in T4; T3 was observed to be reduced only at a higher dose. In other rat studies of 5–91 days, decreases in T4 and T3 were observed, with the former effect being more sensitive (Yu et al. 2009a, 2011; Luebker et al. 2005b; Thibodeaux et al. 2003). The effects were primarily measured on total levels of the hormones, with some studies also measuring effects on levels of free T4 and T3. No effects on TSH were observed in rat studies.

Few mouse studies measured changes in thyroid hormones. A dose-dependent, but transient, decrease in total T4 was observed to be significant at 20 mg/kg bw per day in dams exposed GD 1–17 (Thibodeaux et al. 2003), but no effect on serum T3 or T4 levels was measured in mice exposed to up to 0.166 mg/kg bw per day for 28 days (Fair et al. 2011).

Changes in thyroid hormone levels were observed in rat and mouse pups exposed in utero to PFOS; these effects are described in Section 5.2.5.

No changes in thyroid follicular cell proliferation index was observed in male Sprague-Dawley rats exposed to K^+PFOS (20 or 100 ppm in diet) for 7 days (1.9 or 9.6 mg/kg bw per day), when measured at various timepoints (1 day after cessation of exposure or after recovery periods of 28, 56, or 84 days (Elcombe et al. 2012a).

5.2.2.5 Other Short-term Effects

A wide variety of other short-term effects were observed for PFOS. These effects are described below, albeit only briefly as they occurred at higher levels than immune, hepatic, serum lipid, or thyroid effects.

Decreased body weight (or body weight gain) was a common observation in a wide variety of studies. The effect was observed in rats at ≥0.4 mg/kg bw per day (Goldenthal et al. 1978a; Gortner 1980; Wetzel 1983; Christian et al. 1999; NOTOX 1999; Grasty et al. 2003; Thibodeaux et al. 2003; Luebker et al. 2005a; Butenhoff et al. 2009; Cui et al. 2009; Kawamoto et al. 2011; Xia et al. 2011; Elcombe et al. 2012a); in mice at ≥0.4167 mg/kg bw per day (Yahia et al. 2008; Dong et al. 2009, 2011, 2012b; Era et al. 2009; Wan et al. 2011); and in rabbits at ≥1 mg/kg bw per day (Case et al. 2001. Contributing to this effect might be decreased food consumption, which was observed at ≥0.4 mg/kg bw per day in rats (Goldenthal et al. 1978a; Wetzel 1983; Christian et al. 1999; Thibodeaux et al. 2003; Cui et al. 2009), ≥0.4167 mg/kg bw per day in mice (Yahia et al. 2008; Dong et al. 2011, 2012b), and ≥5 mg/kg bw per day in rabbits (Case et al. 2001).

Few studies demonstrated increases in mortality in adult animals. In monkeys, deaths were observed in all males in the 4.5 mg/kg bw per day group in a 90 day study (Goldenthal et al. 1978b), and in 2 (out of 6) males exposed to 0.75 mg/kg bw per day for 6 months (Seacat et al. 2002). Increased mortality was also observed in rats at ≥6 mg/kg bw per day (Goldenthal et al. 1978a; Wetzel 1983; Grasty et al. 2005b; Cui et al. 2009), and in rabbits at ≥20 mg/kg bw per day (Case et al. 2001).

Other general effects observed included localized alopecia in rats (Christian et al. 1999) and soft stool, diarrhea, anorexia, emesis, and twitching, trembling and convulsions in monkeys (Goldenthal et al. 1978b).

A few neurotoxicity endpoints were observed in PFOS-exposed mice. Worsened performance was observed in neurobehavioural tests, including the water maze (at ≥2.15 mg/kg bw per day [Long et al. 2013], and 3 mg/kg bw per day, but not 6 mg/kg bw per day [Fuentes et al. 2007c]), and transient effects in the open field test (3 mg/kg bw per day) and number of rearings (6 mg/kg bw per day) (Fuentes et al. 2007c). However, the transient effects were both observed only on the same day, leading authors to conclude that the effects might be related to increased anxiety. Increased apoptosis (at ≥2.15 mg/kg bw per day) and glutamate levels (at 10.75 mg/kg bw per day) were observed in the hippocampus (Long et al. 2013). Increased expression of of CaM-KIIα, pCREB, c-fos and c-jun was also observed in rat cortex and hippocampus at ≥1.7 mg/L in drinking water (0.238 mg/kg bw per day using Health Canada's default assumption that 1 ppm in water is equivalent to 0.14 mg/kg bw per day in rats [Health Canada 1994]) (Liu et al. 2010a).

Neurotoxicity was also observed in rats. Reductions in activity and lethargy were observed at ≥5 mg/kg bw per day (Cui et al. 2009). Histological effects in the brain were also observed at ≥20 mg/kg bw per day (Cui et al. 2009), but not at levels of up to approximately 7 mg/kg bw per day (Kawamoto et al. 2011). Co-exposure with ultrasonic stimulation induced tonic convulsion (no tonic convulsion was induced by PFOS alone) after exposure to approximately 7 mg/kg bw per day (Kawamoto et al. 2011).

Renal effects from PFOS exposure were limited to increased BUN in male and female rats (with a LOAEL of 1.33 mg/kg bw per day; Seacat et al. 2003) and increased relative kidney weight at (at ≥5 mg/kg bw per day) in rats (Goldenthal et al. 1978a; Cui et al. 2009).

Respiratory tract effects—including pulmonary congestion, thickened epithelial walls, cell infiltration, and vasodilation—were observed at 5 and 20 mg/kg bw per day, with worsened severity at the high dose (Cui et al. 2009). Laboured breathing and bloodstains around the nose were also reported for the high dose in the study.

5.2.3 Long-term Exposure and Carcinogenicity

Only one chronic bioassay has been performed for PFOS. The study exposed Sprague-Dawley rats to dietary K^+PFOS (0, 0.5, 2, 5 and 20 ppm in feed) for 2 years (mean daily doses: 0, 0.024, 0.098, 0.242 and 0.984 mg/kg bw per day for males; 0, 0.029, 0.120, 0.299 and 1.251 mg/kg bw per day for females) (Butenhoff et al. 2012b). A recovery group (20 ppm Rec.) was also exposed to the high dose diet for the first 52 weeks and then fed with control diet (mean daily doses: 1.144 and 1.385 mg/kg bw per day for male and female respectively). Early sacrifice was also performed at weeks 4 and 14; the observations at these time points are presented throughout Section 5.2 (as Seacat et al. 2003).

The liver was identified as the principal target site in males (LOAEL of 0.5 ppm or 0.024 mg/kg bw per day; no NOAEL identified). The LOAEL was based on significant increased incidence of cystic degeneration in the liver in all dose groups. Other effects in the liver of males at higher doses (≥0.098 mg/kg bw per day) include significant increased incidence and severity of centrilobular hepatocytic hypertrophy, eosinophilic hepatocytic granule, centrilobular hepatocytic pigment, hepatocyte necrosis, and midzonal/centrilobular hepatocytic vacuolation. Most effects were observed to be reversible, as they were observed at levels similar to controls in the recovery group; however, incidence of cystic degeneration and hepatocyte necrosis were similar in the recovery group, indicating that the effect persisted even after exposures had been ceased for one year. Decreased mortality (statistically significant at 5 and 20 ppm) and changes in absolute and relative organ weights in the high dose group (increased in liver and decreased in spleen and left thyroid/parathyroid) were also observed. An increased incidence of interstitial fat infiltration was reported in males at 0.098 mg/kg bw per day (no data available for other doses).

In female rats, no consistent dose–response relationship was observed for non-neoplastic lesions in the liver; a statistically significant increased incidence of several liver lesions was observed at ≥0.120 mg/kg bw per

day for lymphohistiocytic infiltrate, centrilobular hepatocytic hypertrophy, eosinophilic hepatocytic granule, centrilobular hepatocytic pigment, hepatocyte necrosis, periportal hepatocyte vacuolation, and macrophage pigmented infiltrate and decreased periportal hepatocyte hypertrophy. Increased relative (to body weight) brain, kidney, liver and spleen weight were also observed as well as decreased absolute left adrenal weight and relative (to brain weight) left and right adrenal weight.

Decreased serum total cholesterol was observed at several different timepoints in males (14, 17, and 53 weeks), with significance observed only at the high dose (NOAEL of 0.242 mg/kg bw per day, and LOAEL of 0.984 mg/kg bw per day). The effect in females was limited to a transient decrease, with decreases in the three highest dose groups at week 27 only.

Macroscopic observations of livers at the end of the study exhibited enlarged, mottled, diffusely darkened or focally lightened livers in male and female rats given 5 or 20 ppm. No data were available for the other groups (Butenhoff et al. 2012b).

Carcinogenic effects in the study included tumours in the liver, thyroid, and mammary gland. An increased incidence of total hepatocellular adenoma, statistically significant at 20 ppm, was observed in both sexes in rats exposed for 2 years, but not 52 weeks. Thyroid follicular cell tumours (adenomas in males, and adenomas/carcinomas combined in females) were significantly increased in recovery group males and in the second highest exposure group in females (5 ppm or 0.299 mg/kg bw per day). In females, mammary fibroadenoma and fibroadenoma/adenoma combined were increased over controls only in the lowest dose group, and showed a significant negative trend.

The authors noted that serum and liver PFOS levels at the end of study were dramatically lower than after 14 weeks exposure in both sexes. In males, serum levels at terminal sacrifice were 33%, 44%, 51%, and 47% of those measured on Week 14 in the 0.5, 2, 5, and 20 ppm groups, and liver levels were 33%, 36%, 19%, and 33% of Week 14 values in the same dose groups, respectively. The authors suggested that this decline was likely due to chronic progressive nephritis leading to increased urinary excretion of PFOS across all treatment groups. Data on nephritis were not provided by authors, who described the effect as occurring across all treatment groups; however, they stated significant associations were observed between incidence and severity of nephritis in males (but only at one dose in females). Serum PFOS concentrations also increased in approximate proportion to length of dosing between Weeks 4 and 14; however, Week 53 concentrations in the 20 ppm group were similar to those measured on Week 14, suggesting that steady state may have been approached after 14 weeks in the 20 ppm dose group. The serum PFOS levels corresponding to the LOAEL (0.5 ppm in diet) were 4,040 ng/mL at 14 weeks and 1,310 ng/mL at 105 weeks (Butenhoff et al. 2012b).

5.2.4 Genotoxicity

Based on negative results of a large series of in vitro and in vivo short-term tests of genes, chromosomes, or DNA repair, EFSA (2008) and Health Canada (2006) concluded that PFOS and its salts are not genotoxic. More recently published data (see the following subsections) are in agreement with this conclusion.

5.2.4.1 In Vitro Findings

Negative results were obtained in various in vitro assays conducted for PFOS on prokaryotes, namely the reverse gene mutation assay in Salmonella typhimurium (TA100, TA1535, TA1537, TA1538 and TA09 strains; 2 studies) and *Escherichia coli* (WP2uvrA, one study) conducted with/without metabolic activation (S9) and the mitotic recombination test in Saccharomyces cerevisiae (D4 strain, 1 study) (as reviewed by EFSA 2008; as cited in Health Canada 2016). PFOS (tested up to 1,000 µM) had no mutagenic activity in the umu test (Oda et al. 2007).

In human hepatoma HepG2 cells, PFOS (up to 400 µM for 24 h) did not induce ROS generation, DNA single strand breaks or micronuclei (Florentin et al. 2011). In another study of human HepG2 cells, PFOS induced slight ROS generation (0.4–2,000 µM) without generating detectable DNA damage (200 µM) (Eriksen et al. 2010).

PFOS did not induce chromosomal aberrations in cultured human lymphocytes with or without metabolic activation and did not induce unscheduled DNA synthesis (UDS) inprimary cultured rat liver cells (as reviewed by EFSA 2008).

In Syrian hamster embryo (SHE) cells, PFOS induced cell transformation at non-cytotoxic concentrations (0.2–2 µg/mL) and increased the expression of PPARβ/δ (0.2 µg/mL for 1 and 7 days; 2 µg/mL for 7 days), PPARγ (0.02–2 µg/mL for 7 days) and PPARα (20 µg/mL for 7 days). PFOS did not induce DNA damage in the comet assay (Jacquet et al. 2012).

Negative results were also found in different in vitro tests conducted with several PFOS precursors (as reviewed by EFSA 2008).

5.2.4.2 In Vivo Findings

PFOS was negative in the in vivo bone marrow mouse micronucleus assay at single oral doses of 237.5, 450 and 950 mg/kg bw (with sampling at 24, 48 and 72 hours), and several PFOS precursors were found negative in different in vivo tests (as reviewed by EFSA 2008).

A comet assay conducted in *Paramecium caudatum* was negative (Kawamoto et al. 2010).

5.2.5 Reproductive and Developmental Toxicity

The reproductive and developmental database for PFOS is robust (Health Canada 2016). A 2-generational study has been developed in rats (Christian et al. 1999; Luebker et al. 2005a), and reproductive and developmental parameters have been investigated in many one-generation studies in rats, mice, and rabbits. Effects that occurred at the lowest levels in animals exposed in utero included changes in brain structure (≥0.1 mg/kg bw per day), neurobehaviour (≥0.3 mg/kg bw per day), thyroid hormone levels (≥0.16 mg/kg bw per day), and fetal body weight (≥0.1 mg/kg bw per day). The majority of the other effects were observed at ≥1 mg/kg bw per day. Doses described throughout this section refer to maternal doses for animals exposed in utero, unless otherwise specified.

Changes in structure and in levels of various proteins and neurotransmitters in the brain were observed in mice and rats. In Sprague-Dawley rats exposed on GD0–20 to 0, 0.1, 0.6, and 2 mg/kg bw per day by gavage, structural modification of synapses in the hippocampus was observed in all doses (Zeng et al. 2011b). This study also identified decreased mRNA levels of synapsin1, synapsin2, and synaptophysin in the brain at all doses. Brain transcriptional changes—with multiple genes related to long-term potentiation/depression, synaptic transmission, calcium-dependent signal transduction, and phosphatidylinositol signalling pathways—were also observed in rats exposed to 3.2 ppm of PFOS in feed (equivalent to approximately 0.16 mg/kg bw per day using the Health Canada default assumption of 1 ppm in food = 0.05 mg/kg bw per day in rats [Health Canada 1994]) (Wang et al. 2010, 2012). A companion study exposing rats to the same doses on GD2–21 also noted increases in GFAP in the hippocampus and cortex (at ≥0.1 mg/kg bw per day) and IL-1β and TNF-α in the hippocampus (at ≥0.6 mg/kg bw per day) (Zeng et al. 2011a). Changes were observed in the levels of proteins that are important in brain development (CamKII, GAP-43, synaptophysin, and tau, in cerebral cortex and/or hippocampus), in mice exposed to a single dose of 8.7 mg/kg (Johansson et al. 2009). At higher doses (>1 mg/kg bw per day) in rats, changes were observed in choline acetyltransferase activity in prefrontal cortex (Lau et al. 2003) and calcium related signalling molecules (Liu et al. 2010b; as cited in Health Canada 2016).

In addition to changes in the brain, adverse effects from PFOS manifested as neurobehavioural changes at ≥0.3 mg/kg bw per day. The most common effect observed was changes in activity levels in mice (Onishchenko et al. 2011; Johansson et al. 2008; Fuentes et al. 2007a) and rats (Butenhoff et al. 2009), with some evidence that the effect was more pronounced in males (Onishchenko et al. 2011). Other effects observed were neuromotor decrements (worsened screen climb and pull and diminished forelimb grip strength in mice [Fuentes et al. 2007b] and decreased hindlimb strength in rats [Butenhoff et al. 2009), delayed reflex in rats (Christian et al. 1999; Luebker et al. 2005a), and decrements in spatial learning and memory in the water maze test (Liu et al. 2009b) and hidden platform test (Wang et al. 2015) in rats.

Developmental exposure to PFOS resulted in changes to thyroid hormones at similar exposure levels to adult animals. Rat neonates whose mothers were exposed during gestation and lactation to ≥3.2 ppm in food (equivalent to ≥0.16 mg/kg bw per day using Health Canada's default assumption that 1 ppm in food = 0.05 mg/kg bw per day [Health Canada 1994], an assumption that might not be relevant in pregnant or newborn rats) had dose-dependent decreases in total T4 (Wang et al. 2011a; Yu et al. 2009b; Lau et al. 2003). No changes in T3 levels were observed in two rat studies (Yu et al. 2009; Lau et al. 2003), but they occurred at high levels in another (Wang et al. 2011a). An additional neonatal study describing thyroid effects did not see any change in serum TSH in rat offspring, but increases in thyroid follicular epithelial cell proliferation were observed at 1 mg/kg bw per day (Chang et al. 2009). The only effect observed in developmental studies in mice was a decrease in total T4 at ≥5 mg/kg bw per day, but the effect was less consistent than in rats (Lau et al. 2003).

Although effects on the immune system and serum lipid levels were key effects that were well studied in adult mice, rats, and monkeys, very few studies investigated these effects during prenatal exposure. Adult mice exposed in utero to PFOS at 0, 0.1, 1, or 5 mg/kg bw per day had decreases in NK cell activity (at ≥1 mg/kg bw per day in males and 5 mg/kg bw per day in females), decreases in SRBC-IgM response (in males at 5 mg/kg bw per day), and changes in thymic lymphocytic subpopulations (at 5 mg/kg bw per day) (Keil et al. 2008). Increased serum cholesterol and LDL were increased on GD21 in rat fetuses exposed in utero to ≥1.6 mg/kg bw per day, the lowest dose at which this effect was studied (Luebker et al. 2005b). At LD_5, the same study found no effects on serum lipid parameters in pups, but did observe a decrease in liver triglyceride levels.

Increased absolute or relative fetal liver weight was increased in mice at ≥5 mg/kg bw per day (Keil et al. 2008; Lau et al. 2003; Abbott et al. 2009). The effect was also observed in rats (Lau et al. 2003; as cited in Health Canada 2016), but the species was less sensitive than mice (effects were only observed at 20 mg/kg bw per day).

Cardiac mitochondrial injury and increased relative heart weight were observed at 2 mg/kg bw per day in rats exposed in utero (Xia et al. 2011). These effects were not accompanied by changes in heart rate or blood pressure; however, systolic blood pressure was increased in rats exposed prenatally to 18.75 mg/kg bw per day (Rogers et al. 2014). The blood pressure effect in Rogers et al. (2014) was correlated with decreased nephron endowment. The only other effect that was noted in kidney development was decreased kidney weight in mice exposed to 5 mg/kg bw per day (Keil et al. 2008).

Changes suggesting immaturity of lungs were noted in rats exposed in utero to PFOS at ≥2 mg/kg bw per day. Observed histological changes included hemorrhage, thickened interalveolar septum and alveolar walls, focal lung consolidation, inflammatory cell infiltration, and apoptotic cells (Chen et al. 2012; Grasty et al. 2003, 2005). Atelectasis and abnormal expansion of lungs was also observed (Grasty et al. 2003; 2005). Because the pulmonary surfactant profile in offspring was normal and rescue agents (accelerators of pulmonary maturation) did not improve laboured respiration and mortality, the authors thought the latter effects were not due to lung immaturity (Grasty et al. 2005). The only evidence of potential adverse lung

effects in mice pups was the observation of post-delivery cyanosis in some pups exposed to 12.5 mg/kg bw per day (Borg et al. 2010).

A variety of adverse effects were noted on the general health status of animals exposed prenatally to PFOS. Decreased survival or viability, or increased mortality were observed in foetuses or pups at ≥1.6 mg/kg bw per day in rats (Christian et al. 1999; Lau et al. 2003; Luebker et al. 2005a, 2005b; Xia et al. 2011;) and at ≥4.5 mg/kg bw per day in mice (Lau et al. 2003; Yahia et al. 2008; Abbott et al. 2009). Decreased pup body weight or fetal weight were observed at the lowest levels at ≥0.1 mg/kg bw per day in a study of rats (Christian et al. 1999; Luebker et al. 2005a, 2005b). Other studies noted effects at higher levels in rats (at ≥1.6 mg/kg bw per day; Wetzel 1983; Lau et al. 2003; Wang et al. 2011a; Xia et al. 2011; Chen et al. 2012; Rogers et al. 2014), mice (at 6 mg/kg bw per day; Fuentes et al. 2007b; Era et al. 2009), and rabbits (at ≥2.5 mg/kg bw per day; Case et al. 2001). Non-significant growth deficit was also observed in mice at 10 mg/kg bw per day (Lau et al. 2003). Rat pups also appeared pale and delicate at 1.6 mg/kg bw per day (Wang et al. 2011a).

Prenatal PFOS exposure caused developmental landmark delays and structural abnormalities. Delayed eye opening was observed at ≥1 mg/kg bw per day in mice (Lau et al. 2003; Fuentes et al. 2007b; Abbott et al. 2009) and ≥1.6 mg/kg bw per day in rats (Christian et al. 1999; Lau et al. 2003; Luebker et al. 2005a); moreover, abnormalities were observed in the eye lens of rats at ≥1 mg/kg bw per day (Gortner 1980). Other developmental landmark delays occurred in pinna unfolding in rats (Christian et al. 1999; Luebker et al. 2005a) and mice (Fuentes et al. 2007b), and incisor eruption in mice (Fuentes et al. 2007b; Yahia et al. 2008). Skeletal abnormalities were also observed at ≥1 mg/kg bw per day. The effects observed at the lowest levels were sternal defects in mice (Lau et al. 2003; Yahia et al. 2008) and rats (Wetzel 1983; Lau et al. 2003) and incomplete skull closure in rats (Wetzel 1983; as cited in Health Canada 2016). Other effects observed included: cleft palate in mice (Lau et al. 2003; Yahia et al. 2008; Era et al. 2009) and rats (Wetzel 1983; Lau et al. 2003;); rib abnormalities in mice (Yahia et al. 2008) and rats (Wetzel 1983); delayed ossification in mice (Yahia et al. 2008), rats (Wetzel 1983), and rabbits (Case et al. 2001); curved fetus, spina bifida occulta, and tail abnormalities in mice (Yahia et al. 2008); and subcutaneous edema and cryptorchism in rats (Wetzel 1983).

Decreases in reproductive organ weights were observed in animals. A dose-related trend in decreased uterus weight was observed in mice, and was significant at ≥0.166 mg/kg bw per day (Fair et al. 2011). Reduced mean gravid uterine weight was also observed at 10 mg/kg bw per day in rats (Wetzel 1983). These effects occurred in the absence of histological effects. Other reproductive organ weight decreases that were observed were in male rats, affecting absolute seminal vesicle weight (Christian et al. 1999) and relative gonad weight (Cui et al. 2009).

Reproductive effects also resulted from PFOS exposure. The effect at the lowest level was decreased gestation length at ≥0.8 mg/kg bw per day in rats (Christian et al. 1999; Luebker et al. 2005a, 2005b). Other effects observed at higher levels were fewer implantation sites in rats (Luebker et al. 2005a; Christian et al. 1999), reduced litter size in rats (Christian et al. 1999; Xia et al. 2011) and rabbits (Case et al. 2001), and increase in fetal resorptions, dead foetuses, and stillbirths in rats (Luebker et al. 2005a; Wetzel 1983), rabbits (Case et al. 2001), and mice (Lau et al. 2003; Yahia et al. 2008). A significantly reduced lactation index was also observed in rat pups exposed to 1.6 mg/kg bw per day (Christian et al. 1999; Luebker et al. 2005a).

Reproductive effects observed in males were limited to decreased estradiol in male monkeys at 0.75 mg/kg bw per day (Seacat et al. 2002), and decreased serum testosterone levels and epididymal sperm count in male rats exposed to 10 mg/kg bw per day (Wan et al. 2011). Comparing observations across generations in two-generation studies can help to identify emerging patterns in developmental and reproductive effects. Effects in rat pups from the two-generation study (Christian et al. 1999; Luebker et al. 2005a) that were

described throughout this section occurred primarily in the F1 offspring. The F0 dams were exposed to four different doses of PFOS—0.1, 0.4, 1.6, or 3.2 mg/kg bw per day—for 42 days prior to mating, through the mating period (maximum of 14 days), and to day 9 of gestation for rats with c-section delivery, or lactation day 20 for rats with natural delivery. Significantly decreased viability of F1 pups was observed at the two higher doses. At 3.2 mg/kg bw per day, fewer pups were liveborn and more were stillborn. Moreover, the numbers of pups that survived in the first few days of life was lower in the 1.6 mg/kg bw per day group. At the high dose, 0% of pups survived, and at 1.6 mg/kg bw per day, survival was only 66.1% (compared with >98% in controls and lower dose groups). Delays in developmental landmarks—eye opening, pinna unfolding, surface righting, and air righting—were also observed at 1.6 mg/kg bw per day in F1 pups. Maternal toxicity had been apparent in these dose groups, as F0 dams displayed decreases in food consumption and bodyweight gain at ≥0.4 mg/kg bw per day. Due to significant decreases in survival at the two highest doses, exposure to F1 dams was limited to 0.1 and 0.4 mg/kg bw per day. No effects on reproductive outcome (including number of live births and pup survival) were observed in F1 dams/F2 pups; moreover, no maternal toxicity was observed. The only effect observed in the F2 generation was a decrease in pup weight and weight change at 0.4 mg/kg bw per day, for 2 time points only (days 7 and 14). Therefore, decreased pup weight was first observed at a lower level in F2 pups (0.4 mg/kg bw per day) than F1 pups (1.6 mg/kg bw per day); however, the effect was less severe and/or more transient than in F1 pups, where the effect was observed consistently at all time points (days 1–21). Mating and fertility appeared to be unaffected in both generations.

5.3 Toxicokinetics

PFOS is considered chemically unreactive, and it is not metabolized. The oral absorption of PFOS is rapid and complete (Kemper 2003; Hundley et al. 2006; Lau et al. 2007). Once absorbed, PFOS is primarily restricted to plasma and extracellular fluid (Chang et al. 2012) and excreted in urine.

5.3.1 Absorption

PFOS is rapidly and nearly completely absorbed through the gastrointestinal tract. In rats, studies consistently estimated the oral absorption rates of PFOS at >95% after a single dose (4.2 to 20 mg/kg) by gavage (Johnson and Ober 1979; 1999; Cui et al. 2010).

No controlled studies investigating the oral availability of PFOS have been conducted in humans.

No inhalation or dermal studies have reported PFOS kinetics.

5.3.2 Distribution

The highest PFOS concentrations in rats were measured in the liver after a single oral gavage dose of 400 mg/kg (Benskin et al. 2009) and 2 weeks of dietary exposure to 400 mg/kg bw per day (De Silva et al. 2009). This might be due to the binding of PFOS to liver proteins in rat, including the liver fatty acid binding protein (L-FABP) (Luebeker et al. 2002). Similarly, the highest PFOS concentrations were found in liver and serum after intraperitoneal injection of PFOS in female rats (1 or 10 mg/kg bw per day for 2 weeks) (Austin et al. 2003). PFOS was also accumulated primarily in mouse livers after dietary exposure to 0.031 or 23 mg/kg bw per day for 1–5 days (Bogdanska et al. 2011) or a single oral dose of 1 or 20 mg/kg bw (Chang et al. 2012), with liver-to-blood ratios ranging from 2 to 6 (Bogdanska et al. 2011). One of the oral dosing mouse studies also identified storage of PFOS in lungs (lung-to-blood ratios of 1.5–2; Bogdanska et al. 2011). Average liver-to-serum PFOS concentration ratios in monkeys ranged from 0.9 to 2.7, after oral bolus administration of 0.03, 0.15, or 0.75 mg/kg bw per day for 183 days (Seacat et al. 2002). The average percent PFOS dose found in the livers of these monkeys ranged from 4.4 ± 1.6% to 8.7 ± 1.0%.

Few data have been gathered on the human tissues to which PFOS is typically distributed. In tissues taken from human cadavers in the US, the mean liver-to-serum concentration ratio was 1.3, suggesting there is no

extensive binding to liver protein in humans as measured in the rat (Olsen et al. 2003a). Maestri et al. (2006) measured a lung to blood ratio of 1.5 from pooled human samples. Neither cerebrospinal fluid (Harada et al. 2007) nor thyroid (Pirali et al. 2009) have been observed to be relevant partitioning sites for PFOS.

PFOS, as with other perfluoroalkyls, binds to serum albumin and, to a lesser extent, to plasma γ-globulin, α-globulin, α-2-macroglobulin, transferrin and β-lipoproteins (ATSDR 2009; Butenhoff et al. 2012a). Binding of PFOS to the plasma lipoprotein-containing fractions appears to be limited (≤9%) in human, as shown in vitro with the plasma of a human donor (Butenhoff et al. 2012a). PFOS has also been shown to competitively bind to the human thyroid hormone transport protein transthyretin, with less than one-tenth of the T4 affinity (Weiss et al. 2009).

Sex and age have been demonstrated to influence PFOS distribution in rodents and humans. Sex-related differences were observed in maximal serum concentrations of PFOS measured in Sprague-Dawley rats (single oral dose of 2 mg/kg) with females having a 2.5 times higher level than males. At 15 mg/kg, however, the differences were not seen. Chang et al. (2012) also reported slightly slower elimination for PFOS in female rats. After dietary exposure ranging from 4 to 14 weeks (0.5, 2.0, 5.0 and 20 ppm in food), PFOS levels increased proportionally with cumulative dose in both sexes (Seacat et al. 2003). Average serum levels in females were approximately 31–42% higher than in males with liver concentrations reported as being equal. Liu et al. (2011) reported varying distributions of PFOS with age in mice administered a single subcutaneous dose (50 mg/kg) on postnatal day (PND) 7, 14, 21, 28 or 35. The levels of PFOS in the liver increased with age at exposure, whereas the PFOS levels in brain decreased with levels at PND 7 two times that at PND 35. In contrast, the blood PFOS levels did not vary with postnatal age. Serum PFOS levels in humans appeared to be influenced by age and gender in CHMS. The effect was also observed in US studies. In the general US population (NHANES data for 1999–2008), the serum PFOS levels were reported to be significantly higher in males than in females, regardless of age. As age increased, PFOS concentration increased in both sexes and the increase was more pronounced in females than in males (Kato et al. 2011). PFOS blood levels were shown to be influenced by age and gender, with lower PFOS serum in females than in males in the age group 20–50 years; a plausible explanation is menstrual bleeding, as well as gestation and lactation transfer (Harada et al. 2004; Ingelido et al. 2010). The analysis of mother–children data indicated that PFOS levels were on average 42% higher in children than in their mothers, and that this trend persisted until at least 19 years of age. The PFOS child:mother ratios were higher in boys aged 5 years than in girls (Mondal et al. 2012).

PFOS exposure can occur transplacentally and lactationally. Fetal and pup PFOS concentrations in serum and brain were higher than corresponding maternal concentrations in rats exposed to 0.1–1.0 mg/kg bw per day from gestational day (GD) 20 to PND 21 (Chang et al. 2009). Serum concentrations in newborn rats exposed in utero to 1–10 mg/kg bw per day on GD 2–21 mirrored the maternal administered dose and were similar to those in the maternal circulation at GD 21 (Lau et al. 2003). Serum PFOS concentration in mouse pups administered a daily oral bolus from GD 1 to 17 (1, 5, 10, 15 or 20 mg/kg/day) were consistent with the rat data (Thibodeaux et al. 2003). In humans, PFOS cord blood levels have been shown to correlate with maternal serum concentrations (Inoue et al. 2004; Midasch et al. 2007; Needham et al. 2011; Gützkow et al. 2012a); moreover, maternal serum PFOS concentrations have been observed to decrease throughout pregnancy (Fei et al. 2007). PFOS has been measured in breastmilk samples collected worldwide (So et al. 2006; Kärrman et al. 2010; Roosens et al. 2010; Kadar et al. 2011; Sundström et al. 2011). A correlation has been reported for PFOS levels in human milk and maternal serum with average milk to maternal serum concentration ratios ranging from of 0.01 to 0.03 (Liu et al. 2011). PFOS breastmilk concentrations were shown to decrease as the number of infants breast-fed by a mother increased (Tao et al. 2008; Kadar et al. 2011). Most studies reported decreases in PFOS breastmilk (Thomsen et al. 2010) or maternal serum (von

Ehrenstein et al. 2009; Monroy et al. 2008) throughout the lactation period; however, Tao et al. (2008) reported an upward trend for PFOS levels in milk through 6 months of lactation.

5.3.3 Metabolism

The available data indicate that PFOS is not metabolized. Based on the available evidence for PFOA, metabolism is not expected to play a role in the clearance of PFOS (Kemper and Nabb 2005; EFSA 2008; ATSDR 2009).

5.3.4 Excretion

Remarkable species-dependent differences in elimination half-life have been observed, with PFOS remaining in human bodies for a much longer duration than in other species, including non-human primates, rats and mice. Species- and sex-related differences are primarily attributed to elimination kinetics where, at higher doses, the kinetics of PFOS in rodents and primates do not follow one-compartment or simple first-order models (Andersen et al. 2006). The arithmetic mean half-life value for serum elimination of PFOS in humans was calculated as 5.4 years (95% CI: 3.9–6.9 years; range: 2.4–21.7 years) based on data obtained in retired workers (Olsen et al. 2007); no half-life could be found from general population studies. The half-life of PFOS in animals varies depending on experimental protocols, including the duration animals are followed, but is on the order of days to weeks in rodents and months in monkeys.

Urinary and fecal excretion are the primary routes of PFOS elimination in rats (Cui et al. 2010; Chang et al. 2012) and mice (Chang et al. 2012), with most data indicating that urine is a more important route of excretion than feces. One exception was the measurement of slightly higher excretion by fecal than urinary route in rats in the 48 hours after exposure to a single oral dose of 4.2 mg/kg bw; however, excretion was almost 3 times higher in urine in the 89 days after single i.v. dose of 4.2 mg/kg bw in the same study (Chang et al. 2012). PFOS might be subject to extensive enterohepatic recirculation prior to biliary and fecal excretion (Harada et al. 2007; Chang et al. 2012). The relevance of urinary clearance in humans has been questioned, as renal clearance of PFOS was substantially lower than in animals (Harada et al. 2005). In humans, the loss of blood during menstruation may contribute significantly to excretion in women (Harada et al. 2005). Lactation can also be a significant route of excretion in women (von Ehrenstein 2009; Kim et al. 2011a).

5.3.5 Toxicokinetic Models

Several models with varying complexities have been developed to describe the kinetics of PFOS in both experimental animals and humans (Andersen et al. 2006; Tan et al. 2008; Loccisano et al. 2011; 2012a; 2012b; 2013). Due to the non-linear nature of PFOS pharmacokinetics, where faster clearance is seen with high bolus dosing, physiological models can provide an improved means of assessing cross-route and cross-species dosimetry for risk assessment.

The first model developed for PFOS was a biologically-motivated compartmental pharmacokinetic (PK) model for monkeys, which included saturable renal resorption of filtered PFOS (Andersen et al. 2006). Subsequent work to refine the model included the addition of a liver compartment and of time-dependent functions for protein binding and volume of distribution to fit high-dose monkey and rat oral and intravenous plasma, urine and feces kinetic data (Tan et al. 2008). PFOS PBPK models for adult rats (Loccisano et al. 2012a), monkeys (Loccisano et al. 2011) and humans (Loccisano et al. 2011) were built upon the compartmental models; however, the time-dependency function for volume of distribution was removed. Further models for lactation and pregnancy were developed for rats (Loccisano et al. 2012b) and humans (Loccisano et al. 2013). No models have been developed for mice, and no pregnancy and lactation models have been developed for monkeys. The basic structure of the PBPK model was the same for all three species, with only time-dependent changes in physiology included to describe pregnancy and lactation along with the time-dependency for plasma and tissue binding. The models included tissue compartments for gut (for oral/dietary

dosing), skin (human and monkey model only; for dermal dosing), liver, fat, and kidney, with remaining body tissues grouped together (and not divided into richly and poorly perfused compartments). Biliary excretion and fecal elimination of the unabsorbed bolus oral dose or dietary exposure was added to the rat model; moreover, the rat version did not include a fat compartment (which became lumped with the rest of the body) or physiological gut, which was described as a one compartment non-physiological compartment. The PBPK model assumes only the plasma free fraction of PFOS is available for uptake into tissue, excretion or resorption. Elimination from plasma is described as glomerular filtration of the free fraction into a filtrate compartment. The filtered PFOS can either be eliminated in urine or resorbed into the kidney where it can return to systemic circulation. Finally, the rat PFOS model included protein binding in the liver, which was described as being saturable. The models were relatively good at reproducing controlled dosing data for rats (dietary, oral gavage, and IV routes of exposure; Loccisano et al. 2012a), and monkeys (IV and oral gavage routes of exposure; Loccisano et al. 2011). Although no controlled dosing data were available for humans, biomonitoring data (for typically only a single timepoint) were within similar ranges as model simulations (using measured water concentrations for the biomonitored populations, along with assumptions on ingestion patterns; Loccisano et al. 2011).

The Andersen et al. (2006) pharmacokinetic model was modified by Wambaugh and colleagues (2013) by adding a gut compartment for oral absorption and specifying an upper limit on tissue distribution. The authors used the model to translate dose regimes and available LOEL, NOEL, and benchmark dose (BMD) values from 13 *in vivo* studies of PFOS into internal dose metrics (area under the curve, average, and maximum serum concentrations). The data were modelled for cynomolgus monkeys, Sprague-Dawley rats, and CD-1 mice. A Bayesian approach was employed to model ranges of various physiological parameters. Wambaugh et al. (2013) identified relatively good concordance between predicted and measured (at study termination) serum concentrations, with few outliers, and identified that no single dose metric appeared to be best for all adverse endpoints. Dose metrics for points-of-departure (PODs) tended to be similar (with the exception of immune studies, which had lower PODs than other endpoints), indicating consistency between species and most adverse outcomes.

5.4 Mode of Action

Mode of action (MOA) analysis was considered for effects occurring at the lowest PFOS levels (i.e., immune effects in mice, lipid effects in monkeys and mice, liver weight increase in rats and mice, liver histological changes in rats, hepatocellular tumours in rats, and thyroid hormone changes in monkeys, rats, and mice). Only a preliminary evaluation of data could be performed for most of the MOAs; a MOA analysis using recent guidance (Meek et al. 2014) could only be performed for peroxisome proliferation effects on liver endpoints. Based on the MOA analysis, no endpoints were considered to be irrelevant to humans, and the results suggest that the tolerable daily intake approach is the most appropriate method for cancer risk assessment. Results of the MOA evaluations are summarized in this section.

5.4.1 Direct-acting Mutagenicity

Direct-acting mutagenicity was considered as a potential MOA for the development of hepatocellular tumours in rats. Evidence strongly indicates that PFOS is not mutagenic, with or without metabolic activation. PFOS was negative for genotoxicity in a wide variety of *in vitro* and *in vivo* assays. The pattern of PFOS-induced tumours also did not follow that of typical mutagens. For example, mutagens are typically expected to cause tumours in many different organs, but PFOS only induced tumours in the thyroid and liver of rats (Butenhoff et al. 2012b), which were organs that also demonstrated adverse non-cancer effects in rats and other species. Furthermore, mutagens often produce a high incidence of tumours, which occur at early timepoints. In PFOS-exposed animals, hepatocellular tumours were only observed after lifetime duration (and not in rats exposed for 1 year and kept alive for an additional 1 year), and at low incidences (8–12%) (Butenhoff et al. 2012b). Thyroid tumours in the study demonstrated inconsistencies in time–dose relationships and dose–

response relationships (with a significant increase only in the high-dose group exposed for 1 year and not 2 years in males, and a significant increase in a middle dose group in females). The incidence of tumours was still relatively low in most groups, ranging from 7–10% when observed in rats exposed for two years (6–10%), and slightly higher in the male recovery group (23%). These data suggest that low-dose linear extrapolation is not appropriate for PFOS-induced tumours. No further MOA analysis is required for direct-acting mutagenicity, unless contradictory data are published.

5.4.2 Peroxisome Proliferation

Peroxisome proliferation was considered as a potential MOA for hepatocellular tumours in rats, hepatic cystic degeneration in rats, liver weight increase in mice, and increase in serum lipids in monkeys and mice. Some data exist for hepatic peroxisome proliferator-activated receptors (PPAR) activity in rats; however, no studies directly measured PPAR impact on other outcomes. As insufficient data were available to fully apply the evolved Bradford-Hill considerations to evaluate the MOA, the weight of evidence analysis is limited to the evaluation of the dose–response of key events for peroxisome proliferation in rat liver.

Three main key events in the peroxisome proliferation MOA are considered to lead to liver histological effects and hepatocellular tumours. These key events are 1) the activation of hepatic PPARα receptors, which leads to 2) altered cell growth pathways that inhibit apoptosis and/or promote cell replication, eventually leading to 3) hepatocyte proliferation (Corton et al. 2014).

5.4.2.1 Key Event 1 – PPARα Activation

The lowest doses at which PPARα activation was investigated were 0.024–1.25 mg/kg-bw per day, in rats exposed for 4, 14, or 104 weeks (Seacat et al. 2003; Butenhoff et al. 2012b). PPARα activation was not observed to occur at any dose, based on the absence of increase in palmitoyl CoA oxidase activity. Increased PPARα activity was measured after 1 week of exposure at higher doses in rats, with a dose-dependent upregulation of PPARα target genes after exposure to 5 or 20 mg/kg-bw per day (Ye et al. 2012), and an increase in ACOX and 12-OH LAH at 9.65 mg/kg-bw per day (Elcombe et al. 2012b). However, the latter effects were not observed after 1 week of exposure to 1.93 mg/kg-bw per day (Elcombe et al. 2012b). PPAR-activation only occurs at higher concentrations for PFOS than PFOA in in vitro (Takacs and Abbott 2007; Rosen et al. 2013) and in vivo (Rosen et al. 2010) gene expression studies. Furthermore, studies with PPAR-null mice indicated histological effects and hepatic gene expression changes that were similar to mice with active PPAR activity, indicating PPAR-independent effects (Rosen et al. 2010).

5.4.2.2 Key Event 2 – Altered Cell Growth

No studies of markers of altered cell growth pathways could be found.

5.4.2.3 Key Event 3 – Hepatocyte Proliferation

Hepatocyte proliferation was not observed at the lowest doses studied (0.024–1.25 mg/kg-bw per day, for 4, 14, or 104 weeks; Seacat et al. 2003; Butenhoff et al. 2012b). The liver proliferative index was increased, but was not sustained, after exposure to 1.93 or 9.65 mg/kg-bw per day for 1 week (Elcombe et al. 2012b).

5.4.2.4 Comparison of Dose – Response of Key Events and Outcomes

For modes of action to be deemed as relevant for an adverse outcome, dose–response concordance—i.e., the observation of early key events at doses that are lower than or equal to later key events and the adverse outcome—is required. For PFOS, however, the lowest observed doses associated with the adverse outcomes in rats (cystic degeneration: 0.024 mg/kg-bw per day, hepatocellular adenomas: 0.984 and 1.251 mg/kg-bw per day in male and females, respectively) were lower than those at which hepatocyte proliferation was observed (≥1.93 mg/kg-bw per day). This hepatocyte proliferation also might not be associated with

PPARα activation, which was only observed at ≥5 mg/kg-bw per day. Finally, PPARα activation and hepatocyte proliferation were not observed concurrently with cystic degeneration and hepatocellular adenoma in the study where these effects were observed. Because it appears that liver proliferation, hepatocellular adenomas, and cystic degeneration precede PPARα activation, adverse hepatic effects observed in rats exposed for 2 years to PFOS do not appear to be driven by a peroxisome proliferation MOA. For this reason, human relevance of PFOS-induced hepatic effects cannot be discarded. Moreover, hepatic effects do not appear to be specific to rodents—the LOAEL for hepatocellular hypertrophy accompanied by cytoplasmic vacuolation in monkeys (0.75 mg/kg-bw per day; Seacat et al. 2002;) is on the same order of magnitude as in rats (0.242 mg/kg-bw per day; Butenhoff et al. 2012b).

Although insufficient data exist to examine the impact of PPAR activation on changes in serum lipid, thyroid, and immune parameters, peroxisome proliferation is plausible for all endpoints. PPAR activators are known to produce hypolipidemic effects (Corton et al. 2014), and PFOS is similar in structure to fatty acids. In rats, PFOS-induced alterations in gene expression related to fatty acid metabolism and thyroid hormone synthesis and release were of a similar pattern to known PPARα activators (Martin et al. 2007). Some immune effects (weight and cellularity changes in spleen and thymus) were muted in PPAR-null mice (vs. wild-type mice) exposed to PFOA; however, no similar data exist for PFOS, which does not appear to be as strong of a PPAR activator as PFOA. The peroxisome proliferation MOA for these endpoints cannot be fully examined until further data are produced on the impacts of PFOS-induced PPAR activation on immune and serum lipid pathways.

5.4.3 Sex Hormone Disruption

Sex differences were observed in immune response, with males more sensitive than females. However, no studies have been developed to identify whether this effect is associated with sex hormones; therefore, there are insufficient data to evaluate the MOA. PFOS does, however, appear to have some impact on sex hormone disruption—in a variety of in vitro assays of estrogenicity, PFOS did not display direct estrogenic activity, but enhanced the effects of 17β-estradiol in several assays (Sonthithai et al. 2015). If more in-depth studies on the effect of PFOS on sex hormone disruption are performed, this potential MOA could be further investigated.

5.4.4 Immune Suppression

Immune suppression in rats (decrease in IgM and NK cell levels) has been observed at lower doses than those that were tumorigenic. Although NK cells are involved in eliminating cancer cells, no studies investigating the role of PFOS-induced immunosuppression in tumour development have been performed. No detailed analysis for this potential MOA can be performed using current data. If more in-depth studies on the association between PFOS-induced immunosuppression and tumour development are performed, this potential MOA could be further investigated.

5.4.5 Other Modes of Action

Insufficient data exist to allow for the assessment of other potential MOAs considered in the MOA analysis. Some data—particularly in regards to PPAR activation/peroxisome proliferation—exist for other endpoints that were not included in the MOA analysis (i.e., effects that were observed only at higher PFOS exposure levels).

5.5 Summary and Toxicity Reference Value Recommendations

Health Canada (2016) has calculated a tolerable daily intake for PFOS based on the toxicological data summarized in Section 5.0. The following sections summarize how the proposed chronic TRV for PFOS was derived.

5.5.1 Acute Oral Toxicity Reference Value for PFOS

An acute oral TRV could not be derived for PFOS due to lack of appropriate acute toxicity data.

5.5.2 Derivation of Proposed Subchronic Oral Toxicity Reference Value for PFOS

Health Canada has not derived a sub-chronic oral TRV for PFOS.

5.5.3 Derivation of Proposed Chronic Oral Toxicity Reference Value for PFOS

For the purpose of calculating a human health based SSV for PFOS, the tolerable daily intake (TDI = 6 x 10^{-5} mg/kg bw/day, equivalent to 60 ng/kg bw/day) derived by the Drinking Water Group (DWG) of Health Canada (Health Canada 2016) was adopted. A dose-response analysis was conducted by Health Canada (2016) to derive the TDI. It is based on the toxicological review completed in 2013 (Sanexen 2013).

5.5.3.1 Cancer Assessment

The carcinogenicity of PFOS has not been evaluated by IARC. Consistent observations of associations between PFOS exposure and cancers have not been identified in epidemiological studies. Some associations between PFOS and risk of cancer of the bladder, breast, male reproductive organs, and overall cancers were observed; however, the evidence does not support the carcinogenicity of PFOS. The association for bladder cancer was lost after further follow-up, the population demonstrating associations for breast cancer were also exposed to several other chemicals, and associations for male reproductive cancers were not supported by studies of other populations. Therefore, although some evidence of an association between PFOS and the risk of cancer has been observed, the effects were equivocal, and no clear trend could be determined due to limitations in the studies (including small number of cases, confounding, and participant selection bias).

In the sole chronic bioassay performed for PFOS, tumours were observed in the liver, thyroid, and mammary gland of Sprague-Dawley rats (Butenhoff et al. 2012b). Hepatocellular adenoma was observed to be significantly increased in high dose males and females (0.984 and 1.251 mg/kg bw per day, respectively) after 2 years of exposure. Dose–response and temporal patterns for thyroid and mammary gland tumours were less consistent. Thyroid follicular cell adenomas were increased in recovery group males (exposed to 1.144 mg/kg bw per day for 52 weeks), but not those exposed for the duration of the study. Combined thyroid follicular cell adenomas and carcinomas were increased only in females in the second-highest exposure group (0.299 mg/kg bw per day), but not in high-dose females. Finally, incidence of mammary fibroadenoma and combined fibroadenoma/adenoma was increased only in the lowest dose of females (0.029 mg/kg bw per day), but no other groups.

Although the mode of action for PFOS-induced tumours has not yet been elucidated, the weight of evidence more strongly suggests that PFOS is a non-mutagenic compound. For this reason, a threshold approach is the most appropriate method for deriving a TDI for PFOS.

Hepatocellular tumours were selected as the critical effect for the cancer risk assessment, as it is the cancer endpoint with the most consistent dose–response relationship. In males, tumours were only classified as hepatocellular adenomas; in females, the majority of tumours were hepatocellular adenomas, with one incidence of hepatocellular carcinoma in the 2-year high-dose group. Incidence of these tumours in male and female rats is presented in Table 3.

Table 3: Incidence of Hepatocellular Tumours in Butenhoff et al. (2012b; as cited in Health Canada 2016)

Treatment Group (ppm)	Males – hepatocellular adenomas only		Females – hepatocellular adenoma & carcinoma combined	
	Dose (mg/kg bw per day)	Incidence (%)	Dose (mg/kg bw per day)	Incidence (%)
0	0	0/60 (0%)	0	0/60 (0%)
0.5	0.024	3/50 (6%)	0.029	1/50 (2%)
2	0.098	3/50 (6%)	0.12	1/49 (2%)
5	0.242	1/50 (2%)	0.299	1/50 (2%)
20	0.984	7/60 (12%)*	1.251	5/60 (8%)*
20 ppm recovery	1.144	0/40 (0%)	1.385	2/40 (5%)

*p≤0.05

Benchmark dose (BMD) modelling was performed separately for males and females. The Log Logistic model provided the best fit (i.e., lowest Akaike information criterion) for both males and females. Estimated BMD values in males were BMD_{10} of 2.25 mg/kg bw per day and $BMDL_{10}$ of 0.318 mg/kg bw per day; in females, the values were BMD_{10} of 1.81 mg/kg bw per day and $BMDL_{10}$ of 0.732 mg/kg bw per day. Due to dose–response curves that were less than ideal (i.e. incidence did not increase progressively as dose increased), model fits were somewhat weak, particularly in males (p-values for Log Logistic models were 0.44 in males and 0.77 in females). However, the model fit was considered to be sufficient based on recommended criteria (i.e., p-value >0.10) (US EPA 2012). As the $BMDL_{10}$ of 0.318 mg/kg bw per day for males is more conservative than the corresponding value in females, this has been selected as the point-of-departure for the calculation of the TDI for cancer. Because the test material used in the study was only 86.9% pure, the adjusted $BMDL_{10}$ to account for actual PFOS concentration is 0.276 mg/kg bw per day.

To reflect the large interspecies differences in pharmacokinetics, the human-equivalent point-of-departure (POD_{HEQ}) can be calculated by dividing the $BMDL_{10}$ by the AK_{UF}, as follows:

$$\text{[illegible]} = \frac{0.276 \text{ [illegible]}}{10} = 0.028 \text{ [illegible]}$$

where:

- 0.276 mg/kg bw per day is the $BMDL_{10}$ for hepatocellular tumours in male rats (Butenhoff et al. 2012b;); and
- 10 is the dose-specific AK_{UF} for rats in the 0.1 mg/kg bw per day range

Using the calculated POD_{HEQ}, the cancer TDI was calculated as follows:

$$\text{[illegible]} = \frac{0.276 \text{ [illegible]}}{25} = 0.0011 \text{ [illegible]}$$

where:

- 0.028 mg/kg bw per day is the POD_{HEQ} calculated above; and
- 25 is the composite uncertainty factor, as described below

The composite uncertainty factor of 25 is the product of 2 components: the interspecies uncertainty factor (2.5) and intraspecies uncertainty factor (10). A value of 2.5 is used to reflect only the toxicodynamic component of the default interspecies uncertainty factor, because the toxicokinetic differences between rats and humans were already incorporated when calculating the POD_{HEQ}. A default value of 10 was applied for the intraspecies uncertainty factor. The default value was assumed to be sufficient in the absence of data on intraspecies differences. Although large differences in pharmacokinetics are known to occur between species, insufficient data on the mechanism of PFOS excretion precludes investigations of whether the pharmacokinetic variability would also be wide within the human population. In the one study of human half-life of PFOS, the range between the lowest and highest values is 10-fold. If further studies of PFOS consistently indicate a 10-fold difference in pharmacokinetics within the population, a higher intraspecies uncertainty might be warranted to ensure that pharmacodynamic differences between humans are also quantitatively addressed.

5.5.3.2 Non-Cancer Assessment

Although epidemiological evidence has shown an association between the exposure to PFOS and an increased risk of multiple health outcomes, such as reproductive, developmental, and immunological effects, a point-of-departure (POD) cannot be derived from the studies due to their limitations, including in terms of study design, bias and confounders.

The effect observed at the lowest exposure levels was immune system suppression in mice. The lowest LOAEL for immunosuppression data classified by IPCS (2012) as providing the strongest weight of evidence for immunotoxicity was suppression of SRBC-specific IgM in mice at ≥0.00166 mg/kg bw per day (Peden-Adams et al. 2008). Immune system effects were excluded from the quantitative risk assessment due to inconsistencies in NOAELs and LOAELs among studies and uncertainty of the importance of observed effects to human health, both of which will be expanded upon in this appendix. Inconsistencies were observed in the effective PFOS doses for immune function endpoints: the suppression of SRBC-specific IgM in B6C3F1 mice in Peden-Adams et al. (2008) was observed at ≥0.00166 mg/kg bw per day, whereas the LOAEL in C57Bl/6 mice was 0.0833 mg/kg bw per day, with no significant changes observed at 0.0083 mg/kg bw per day (Dong et al. 2009) or 0.0167 mg/kg bw per day (Dong et al. 2011). Moreover, NK cell activity was actually increased at 0.0166 mg/kg bw per day in B6C3F1 mice (Peden-Adams et al. 2008); in C57Bl/6 mice, the effect was non-monotonic, with increased activity at low doses (significant at 0.0833 mg/kg bw per day), and significant decreases at higher doses (0.833 and 2.083 mg/kg bw per day) (Dong et al. 2009). An additional study identified increased mortality from influenza A infection in mice at 0.025 mg/kg bw per day (Guruge et al. 2009); however, this effect was not studied in other species. The adversity of IgM suppression and changes in NK cell activity is also debatable—although these effects indicate immune system changes, it is unclear whether small variations in these measures are sufficient to result in adverse health effects in humans. Of note for discussion of clinical importance in humans is the Grandjean et al. (2012) study, which demonstrated that despite decreased vaccine-specific immunoglobulin response in PFOS-exposed children, the number of children with immunoglobulin levels below the clinically-protective level was low. Moreover, mice appear to be more sensitive than other species, as the LOAEL for immunosuppression was several orders of magnitude higher in the lone rat study, at 3.21 mg/kg bw per day (Lefebvre et al. 2008). In humans, evidence of immunosuppression is inconsistent—associations are observed between PFOS levels and decreases in antibodies against some (but not all) illnesses, and the influence of PFOS exposure on clinical immunosuppression (i.e., incidence of illnesses) appears to be more tenuous. Therefore, although low PFOS doses appear to be associated with immunosuppression, the data are not considered to be presently reliable for use as a key study for the PFOS assessment. Further explorations should be performed to address the nearly two orders of magnitude difference in LOAELs in the studies before these endpoints can be reliably considered as a basis for a risk assessment.

The adverse effect observed at the lowest level (other than the IgM and NK-cell effects in Peden-Adams et al. 2008) was liver cystic degeneration observed in male Crl:CD(SD)IGS BR rats exposed for 104 weeks in feed (Butenhoff et al. 2012b). This effect was observed in a robust study, with 4 treatment groups ($n \geq 55$) and an additional high-dose recovery group ($n = 40$); however, it is not proposed as critical effect for the risk assessment. The endpoint is a common benign, spontaneous lesion in aging rats, particularly males (Bannasch and Zerban 1997; Karbe and Kerlin 2002), which has been classified by some pathologists as a benign neoplasm (Bannasch 2003). Cystic degeneration only rarely occurs in other mammals, including humans (Bannasch and Zerban 1997; Karbe and Kerlin 2002). Although cystic degeneration can be associated with foci of cellular alteration or tumours (Karbe and Kerlin 2002), the progression in PFOS-exposed animals does not follow that of the more serious histological changes. Moreover, the incidence of cystic degeneration was similar among exposure groups, ranging from 27–38% with no dose–related increases, and occurring in similar levels in high-dose rats exposed for 2 years versus recovery rats (33 vs. 38%). The frequency of cystic degeneration in most groups is within the range of spontaneous development in male rats, which is as high as 34% (Karbe and Kerlin 2002).

Hepatocellular hypertrophy was first observed at one dose higher than the LOAEL for cystic degeneration (0.098 mg/kg bw per day) in the Butenhoff study, and incidence increases in a dose-related manner. Although hepatocellular hypertrophy can sometimes be considered an effect that is adaptive rather than adverse in its own right, evidence of other histological effects in the liver at higher concentrations provide an indication of their progression upon continued exposure (ECETOC 2002; Hall et al. 2012; as cited in Health Canada 2016). Clearly adverse histological effects (including cytoplasmic vacuolation) were observed in livers of male rats beginning at the next dose level (0.242 mg/kg bw per day) in the study. Although hepatocellular hypertrophy occurs at one dose level lower than the clearly adverse histological effects, the effect is proposed as a critical effect for this assessment, as it might be a sensitive indicator of the potential for the progression of adverse histological effects. Moreover, the LOAELs were the same for both hepatocellular hypertrophy and cytoplasmic vacuolation in rats from the Butenhoff study that were sacrificed early (after 4 or 14 weeks, with LOAELs of 0.34–0.37 mg/kg bw per day; Seacat et al. 2003; a) and female rats exposed for 2 years (0.299 mg/kg bw per day; Butenhoff et al. 2012b). Hepatocellular hypertrophy accompanied by cytoplasmic vacuolation was also observed in monkeys, with a NOAEL and LOAEL of 0.15 and 0.75 mg/kg bw per day, respectively. Therefore, increased liver weight and hepatocellular hypertrophy are considered in the dose–response assessment—despite their potential to be adaptive, rather than adverse, effects—as a means of preventing the more serious histological effects observed in other studies or at higher doses. The NOAEL of 0.024 mg/kg bw per day was adjusted to a value of 0.021 mg/kg bw per day to account for decreased purity of the test material, which was only 86.9%.

The use of conservative endpoints for liver effects is not contradicted by epidemiology studies. Human studies demonstrated weak and inconsistent evidence of alterations of hepatic enzymes due to PFOS exposure, with positive, negative, and absent associations for hepatic parameters, depending on the study. Associations between changes in ALT levels of former perfluoroalkyl workers (3M plant) and geographically exposed individuals (included in the C8 project) and median PFOS serum levels ranging from 18 to 366 ng/mL have been been reported (Gallo et al. 2012; Olsen et al. 2012); the ALT levels were increased in the environmentally-exposed population and decreased in the occupationally-exposed. No effect on liver enzyme levels was observed in a cross-sectional study of PFOS workers with serum levels in the range of 20–2,110 ng/mL (Olsen et al. 2003b).

The serum values in the study with positive results are one to two orders of magnitude lower than the serum NOAEL and LOAEL values for the Butenhoff study (1,310 and 7,600 ng/mL, respectively).

Changes in thyroid hormone levels—which were observed in monkeys, rats, and mice—are also proposed as a critical effect for this analysis. The observed effects were typically decreases in T3 and T4 that were often

observed at the lowest doses in studies. Corresponding increases in TSH were observed in a 26-week study of cynomolgus monkeys, but not in the rodent studies. Authors of a 26-week study of cynomolgus monkeys (Seacat et al. 2002) concluded that a LOAEL for thyroid hormone changes was 0.75 mg/kg bw per day; however, Health Canada (2013c) performed a statistical reanalysis of the data from Seacat et al. (2002) that allowed for improved interpretation of measures at multiple timepoints. The reanalysis identified dose effects for decreases in total T3 in both sexes and total T4 in females only, and dose–time effects for total T3, total T4, and TSH. The LOAEL and NOAEL values for changes in thyroid hormone levels as identified by the reanalysis were 0.15 and 0.03 mg/kg bw per day, respectively. Most rat studies had no NOAEL; the lowest LOAELs were in a similar range to the monkeys. As the NOAEL of 0.03 mg/kg bw per day from the 26-week monkey study is lower than the NOAEL for hepatocellular hypertrophy, thyroid hormone changes are considered as a potential critical effect for this assessment. Effects on thyroid hormone levels were not studied in many mouse studies, but decreases in T4 were observed only at higher levels (with the lowest LOAEL of 5 mg/kg bw per day in pups exposed in utero [Lau et al. 2003]). The chronic study of rats (Butenhoff et al. 2012b) did not identify any histological changes to the thyroid; however, the study did not explore changes in thyroid hormone levels, which can impact various systems in the body even in absence of structural changes to the thyroid. Epidemiology studies do not indicate any clear trends in PFOS-induced thyroid hormone changes—although some decreases in T3 and T4 were observed in association with increased PFOS levels, other studies indicated positive or absent associations.

Several of the studies identifying decreases in T3 and T4 levels were one-generation studies (primarily in rats), with observations of thyroid hormone level changes in both dams and pups. These thyroid hormones play an important role in development of fetal organs, including that of the central nervous system, with deficiencies observed to result in worsened neurobehavioural outcomes in animals and humans (Pop et al. 1999; Koibuchi and Chen 2000; Morreale de Escobar 2004; Williams 2008; Delahunty et al. 2010; Gilbert et al. 2012; Schroeder and Privalsky 2014). Several studies have provided some evidence of neurodevelopmental effects resulting from PFOS exposure (including changes in the brain ultrastructure, gene and protein expression, and learning abilities in rats, and motor behaviour in both rats and mice), with many LOAELs in a similar range to those observed for thyroid effects. In the one study (in rats) that investigated both thyroid and neurodevelopmental effects (Lau et al. 2003), lower T4 levels were observed in conjunction with small decreases in prefrontal cortex choline acetyltransferase levels (which is sensitive to thyroid hormone status), but no changes in learning and memory behaviours were noted. Although several studies indicate changes in motor behaviour in rats and mice at doses of 0.3–0.75 mg/kg bw per day (Johansson et al. 2008; Butenhoff et al. 2009; Onishchenko et al. 2011; Wang et al. 2015), weaknesses in each of the studies preclude their use as critical studies for these low doses. Study design affected the mouse studies, as Johansson et al. (2008) only provided the dose on a single day, and Onischenko et al. (2011) only contained a single dose group. The rat studies had inconsistent results. In Butenhoff et al. (2009), changes in motor activity were only observed on a single day, which was different in males and females (only at PND 17 in males exposed to 0.3 and 1 mg/kg bw per day, and only at PND 21 in females exposed to 1 mg/kg bw per day, with no effects in either sex at PND 13 or 61). In the Wang et al. (2015) study, rat pups were exposed in utero, lactationally, or both to 5 and 15 mg/L in drinking water (equivalent to 0.7 and 2.1 mg/kg bw per day using Health Canada's [1994] assumption of 1 ppm in water = 0.14 mg/kg bw per day in rats, which might not be relevant for pregnant or lactating dams). Effects on learning ability were observed in both dose groups, but more consistently at the high dose; at the low dose, changes were observed at fewer measurement days and were observed in the groups exposed only in utero or lactationally, and not in the group exposed over both periods. In cross-sectional epidemiological studies, although one study reported a positive association between increased PFOS levels and neurodevelopmental effects (reported ADHD), no clear relationships were observed for this endpoint in limited and equivoqual epidemiological evidence; no associations were observed for other neurodevelopmental milestones. If further studies demonstrate

consistency of effects at low levels, the endpoint could be considered as a potential critical effect for PFOS exposures; in the absence of consistent effects at low levels, a TDI based on liver or thyroid effects is assumed to be sufficiently protective of neurobehavioural changes.

Changes in serum lipid levels were also observed around the levels at which liver and thyroid effects occur. Typical observed changes were decreases in total cholesterol, HDL, and triglycerides. The lowest dose at which serum lipid changes were observed was in the 26-week study of Cynomolgus monkeys, where decreases in HDL were observed at 0.03 mg/kg bw per day (i.e., the NOAEL for the previously-described thyroid effects). The lowest LOAEL for mice was 0.166 mg/kg bw per day (Fair et al. 2011), and for rats was 0.4 mg/kg bw per day (Luebker et al. 2005b). These effects are important for consideration during the assessment of PFOS risks, as epidemiology studies tend to demonstrate minor positive (albeit inconsistent, and of questionable clinical importance) associations between PFOS and serum cholesterol levels. Because inconsistencies in effect were observed between the two databases, and within the epidemiology database, and clear dose–response relationships were absent in the animal studies, quantitative assessments were not performed for serum lipid effects. Based on the present database, a TDI based on liver or serum effects is assumed to be sufficiently protective of lipid changes.

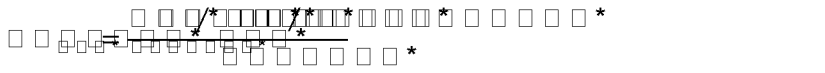
To reflect the large interspecies differences in pharmacokinetics, POD_{HEQ} are calculated for both of the proposed critical effects, as follows:

where:

- X mg/kg bw per day is the point-of-departure associated with the NOAEL for hepatocellular hypertrophy or thyroid hormone changes described above; and
- AK_{UF} is the appropriate dose- and species-specific adjustment factor (as described in Health Canada 2016)

Two different AK_{UF} values were applied for the assessments. Both of the LOAELs were <0.1 mg/kg bw per day; therefore, the corresponding AK_{UF} was applied for each species. An AK_{UF} value of 14 was used for rats, and a value of 4 was used for monkeys, as described in.

Using the calculated POD_{HEQ}, the non-cancer TDIs are calculated as follows:



where:

- X mg/kg bw per day is the POD_{HEQ} calculated for each critical effect, as described above; and
- UF is the composite uncertainty factor, as described below

The composite UF varied based on the effect. For all PODs, an interspecies uncertainty factor of 2.5 was used to reflect only the toxicodynamic component of the default interspecies uncertainty factor, because the toxicokinetic differences between animals and humans were already incorporated when calculating the POD_{HEQ}. Likewise, default values of 10 were applied for the intraspecies uncertainty factor for all PODs. The default value was assumed to be sufficient in the absence of data on intraspecies differences. Although large differences in pharmacokinetics are known to occur between species, insufficient data on the mechanism of PFOS excretion precludes investigations of whether the pharmacokinetic variability would also be wide within

the human population. In the one study of human half-life of PFOS, the range between the lowest and highest values is 10-fold. If further studies of PFOS consistently indicate a 10-fold difference in pharmacokinetics within the population, a higher intraspecies UF might be warranted to ensure that pharmacodynamic differences between humans are also quantitatively addressed. An uncertainty factor of 3 was also applied to reflect that the longest duration at which effects on thyroid hormone levels were explored was a 26-week study in monkeys (Seacat et al. 2002), which is only a fraction of the animal's lifetime. A value of 3 was selected rather than the full value of 10 because the LOAELs for shorter duration studies in rats were similar to those in subchronic studies; however, a subchronic-to-chronic uncertainty factor was still necessitated, despite this observation, as the Health Canada (2013c) reanalysis of data identified a statistically significant time–dose effect for thyroid endpoints. The uncertainty factor was not required for hepatocellular hypertrophy, which was observed in a chronic study. The POD_{HEQ} and TDIs for each critical health effect are calculated and presented in Table 4 below:

Table 4: Calculation of Non-cancer POD_{HEQ} and TDI for Each Critical Health Effect

Study	Hepatocellular hypertrophy Butenhoff et al. 2012b; as cited in Health Canada 2016	Thyroid hormone changes Seacat et al. 2002; as cited in Health Canada 2016
NOAEL (mg/kg bw per day)	0.021	0.03
AK_{UF}	14	4
POD_{HEQ} (mg/kg bw per day)	**0.0015**	**0.0075**
Composite UF	25	75
TDI (mg/kg bw per day)	**0.00006**	**0.0001**

The TDIs calculated for the two critical effects are similar, with a slightly lower value for hepatocellular hypertrophy in rats. For this reason, hepatocellular hypertrophy is used as the basis of the TDI, but is further quantitatively supported by the TDI for thyroid effects in monkeys.

5.5.3.3 Comparison of Cancer and Non-cancer Assessment

The TDI for the non-cancer assessment, which was 0.00006 mg/kg bw/day using data of histological changes in rat liver, is more conservative than the TDI for hepatocellular tumours of 0.0011 mg/kg bw/day. The proposed TDI of 0.00006 mg/kg bw/day that was derived for non-cancer effects is therefore considered to be sufficiently protective of the carcinogenic effects of PFOS.

6.0 CALCULATIONS FOR HUMAN HEALTH SOIL SCREENING VALUES FOR PFOS

The information below is reproduced from Sanexen 2015.

The TDI of 0.00006 mg/kg bw/day derived for chronic oral exposure was used for the derivation of the SSV. Details of the study on which this TDI was based are summarized in Section 5.5.3.2. The input parameters used to derive the SSVs are presented in Table 5.

Table 5: Soil Screening Value Calculation Input Parameters

Acronym	Description	Land Use[a]		
		Agr. and Res./Park.	Commercial	Industrial/ Commercial without Toddler
TDI	Tolerable Daily Intake (mg/kg bw/day) per oral route of exposure (Health Canada 2016)	6×10^{-5}	6×10^{-5}	6×10^{-5}
EDI	Estimated Daily Intake (mg/kg bw/day) (Sanexen 2015)	3.8×10^{-6}	3.8×10^{-6}	2.3×10^{-6}
SF	Soil Allocation Factor (CCME 2006, default - unitless)	0.2	0.2	0.2
BW	Body Weight (CCME 2006 – kg)	16.5	16.5	70.7
AF_G	Relative Absorption Factor for PFOS across the gut (unitless)	1	1	1
SIR	Soil Ingestion Rate (CCME 2006 – kg/day)	8×10^{-5}	8×10^{-5}	2×10^{-5}
AF_S	Relative Absorption factor for PFOS across the skin (unitless)	0.1	0.1	0.1
SR	Soil Dermal Contact Rate (CCME 2006 – kg/day)[b]	6.9×10^{-5}	6.9×10^{-5}	1.14×10^{-4}
AF_L	Relative Absorption Factor for PFOS across the lung (unitless)	1	1	1
IR_S	Soil Inhalation Rate (kg/day)[c]	6.3×10^{-9}	6.3×10^{-9}	1.3×10^{-8}
ET_1	Exposure Term 1 (CCME 2006, default - unitless)	1	0.66	0.66
ET_2	Exposure Term 2 (CCME 2006, default - unitless)	1	0.42	0.42
BSC	Background Soil Concentration (assumed - mg/kg)	0	0	0
SSV_A	Soil Screening Value for agricultural land use (calculated, mg/kg)	2.1	2.1	2.1

a: Agr.: Agricultural, Res./Park.: Residential/Parkland.
b: Soil Dermal Contact Rate = (hands surface area × soil loading to exposed skin of the hands) + (arms surface area × soil loading to exposed skin of the arms) + ([toddler only] legs surface area × soil loading to exposed skin of legs)
c: Value derived from the daily inhalation rate provided by Health Canada (2010; as cited in Sanexen 2015) for the critical receptor, assuming the airborne concentration of suspended soil particulate above a contaminated site is 7.6×10^{-10} kg/m^3.

The human health SSV for direct exposure was derived using the following formula (CCME 2006):

$$SSV = \frac{(TDI * EDI) \cdot SAF \cdot BW}{[(AF_G \cdot SIR) + (AF_L \cdot IR_S \cdot ET_2) + (AF_S \cdot SR)] \cdot ET_1} + BSC$$

6.1 Agricultural and Residential/Parkland Land Use

All human age groups are considered for an agricultural and residential/parkland land use scenarios. The receptors are assumed to be present at the property 24 hours per day, 365 days per year. The most sensitive receptor for agricultural and residential/parkland land use is a toddler (age 7 months – 4 years) for threshold (non-carcinogenic) contaminants. The SSV for the agricultural and residential/parkland land use scenarios were derived based on a toddler.

$$\text{[illegible]} \equiv \text{[illegible]} * \frac{(6 \times 10^{-5} - 3.8 \times 10^{-6}) \times 0.2 \times 16.5}{[(1 \times 8 \times 10^{-5}) + (1 \times 6.3 \times 10^{-9} \times 1) + (0.1 \times 6.9 \times 10^{-5})] \times 1} + 0$$

$$\text{[illegible]} \equiv 2.1 \text{ [illegible]} / \text{[illegible]} * *$$

6.2 Commercial Land Use

All human age groups are considered for a commercial land use scenario. The receptors are assumed to be present at the property 10 hours per day, 5 days per week, 48 weeks per year. The most sensitive receptor for commercial land use is a toddler (age 7 months – 4 years) for threshold (non-carcinogenic) contaminants. The soil screening value for the commercial land use scenario was derived based on a toddler.

$$\text{[illegible]} \equiv \text{[illegible]} * \frac{(6 \times 10^{-5} - 3.8 \times 10^{-6}) \times 0.2 \times 16.5}{[(1 \times 8 \times 10^{-5}) + (1 \times 6.3 \times 10^{-9} \times 0.42) + (0.1 \times 6.9 \times 10^{-5})] \times 0.66} + 0$$

$$\text{[illegible]} \equiv 3.2 \text{ [illegible]} / \text{[illegible]} * *$$

6.3 Industrial/Commercial without a Toddler Land Use

Industrial/commercial without a toddler land use is generally associated with restricted access to adults. The receptors are assumed to be present at the property 10 hours per day, 5 days per week, 48 weeks per year. The most sensitive receptor for industrial/commercial without a toddler land use is an adult (age ≥ 20 years) for threshold (non-carcinogenic) contaminants. The soil screening value for the industrial/commercial without a toddler land use scenario was derived based on an adult.

$$\text{[illegible]} \equiv \text{[illegible]} * \frac{(6 \times 10^{-5} - 2.3 \times 10^{-6}) \times 0.2 \times 70.7}{[(1 \times 2 \times 10^{-5}) + (1 \times 1.3 \times 10^{-8} \times 0.42) + (0.1 \times 1.14 \times 10^{-4})] \times 0.66} + 0$$

$$\text{[illegible]} \equiv 39.4 \text{ [illegible]} / \text{[illegible]} * *$$

6.4 Indirect Exposure Pathways and Check Mechanisms

In addition to the direct soil contact pathways (via ingestion, inhalation and dermal contact with surface soil), indirect exposure pathways and CCME check mechanisms were also considered (CCME 2006). The primary indirect exposure pathways are the migration of soil contaminants into groundwater used as drinking water and the volatilization of soil contaminants into indoor air. The check mechanisms are for offsite migration of contaminants from commercial and industrial sites to more sensitive neighbouring properties and for exposure from ingestion of food grown on contaminated soils.

6.4.1 Protection of Groundwater

The CCME protocol provides equations to develop soil quality guidelines for the protection of potable groundwater (SGQ_{PW}). For PFOS, sorption is the only chemical-specific attenuation mechanism in soil and groundwater since PFOS does not volatilize or biodegrade (EC 2013; OECD 2002;). Other attenuation mechanisms are purely based on hydrogeological and hydrological conditions. On this basis, Koc is a key

parameter to derive an SQG_{PW} for PFOS. However, the level of protection afforded by an SQG_{PW} may not be adequate because the sorption of PFOS is highly variable, with reported Koc values varying from 229 to 6310 L/kg (Franz Environmental Inc. 2014).

Consequently, no SQG_{PW} or SSV_{PW} was derived. Nevertheless, if groundwater is used for human consumption at a PFOS contaminated site, this pathway should be assessed on a site-specific basis (groundwater samples should be analyzed and compared to available drinking water guidelines to ensure the protection of human health from potable water).

6.4.2 Volatilization of Soil Contaminants into Indoor Air

Volatile organic compounds can migrate from soil into the basements of buildings. Vapours may be released from soil to the outside air at the ground surface, in addition to entering buildings. However, since buildings are enclosed spaces and are often under-pressured due to heating, the migration of vapours into buildings poses a much greater health risk than migration of vapours to the outdoors. PFOS is essentially non-volatile; therefore, the indoor vapour inhalation pathway is not considered to be significant in the derivation of soil screening values.

6.4.3 Off-Site Migration Check

Although soil quality guidelines for commercial and industrial sites consider on-site exposure only, wind and water erosion of soil and subsequent deposition can transfer contaminated soil from one property to another. Soil screening values for the offsite migration check were derived using the following formula (CCME 2006):

$$\square = 14.3 \times \square + 13.3 \times \square \quad ***$$

$$\square = 30.5 \square / \square \quad ** \square *$$

Where:

$SSV_{OM\text{-}HH}$ = human health soil quality guideline for off-site migration (i.e., the concentration of substance in eroded soil) (mg/kg)

SSV_A = soil quality guideline (SSV_{HH}) for the agricultural land use (mg/kg)

BSC = background concentration of PFOS in the receiving soil (mg/kg)

6.4.4 Human Food Consumption Check

The check mechanism for consumption of produce, meat and milk is described in CCME (2006) and is a required pathway for biomagnifying substances. Data on uptake of PFOS by plants from soil is sparse, as is information on biotransfer of PFOS from soil to meat and dairy. Therefore, the check mechanism could not be calculated.

7.0 DATA GAPS, UNCERTAINTIES AND LIMITATIONS

The SSVs calculated for PFOS are based on direct contact pathways with soil. As the sorption of PFOS related substances is expected to be highly variable based on the range of reported Log K_{oc} values, a SSV protective of groundwater as a source of drinking water could not be derived. However, if groundwater is used for human consumption at a PFOS-contaminated site, this pathway should be assessed on a site-specific basis (groundwater samples should be analyzed and compared to available drinking water guidelines to ensure the protection of human health from potable water).

The SSVs are also not protective of consumption of produce, meat and milk as data on uptake of PFOS by plants from soil is sparse, as is information on biotransfer of PFOS from soil to meat and dairy products (Sanexen 2015).

Although there were limited chronic toxicological studies available for PFOS, Health Canada considered the studies to be sufficient to calculate a TRV.

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